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TREATMENT OF THYROTOXICOSIS WITH ^{131}I

A REVIEW OF 500 CASES

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The treatment of thyrotoxicosis with ^{131}I is now a well-established procedure. In the sixteen years since Hertz and Roberts (1942) and Hamilton and Lawrence (1942) introduced therapy with radioactive iodine, the use of this technique has spread enormously, and ^{131}I is certainly the radioactive isotope most extensively used in clinical practice. As a result, much published work has accumulated on the subject. As early as 1953 Seed and Jaffé analysed 1,720 cases from the collective results of all papers published up to April, 1952. These came from many centres in North America and Europe, and included many criteria for the selection of cases and different methods of treatment. The reports which have appeared vary from the study of small groups of patients treated by detailed techniques (Bauer and Blahd, 1957) to reports on the results obtained from the use of simple methods involving the minimum of equipment and measurement (Macgregor, 1957).

The techniques used in an endeavour to obtain satisfactory results differ greatly. Fraser *et al.* (1954) have combined a single-dose method with antithyroid drug and thyroxine premedication. On the other hand, Williams *et al.* (1949) have chosen to give small and repeated doses of the isotope. In spite of this wide variation there is little evidence that there is much difference in the final outcome. It is clear that some of the factors influencing the response of the thyroid to ^{131}I therapy are still little understood and remain uncontrolled. The difficulties and uncertainties with this form of treatment have been reviewed by Pochin (1958).

The present report describes the results obtained in 500 thyrotoxic patients treated with ^{131}I in Sheffield. It is thus an expansion of the two previous reports from this centre, in which the results in 20 and 140 patients were recorded (Blomfield *et al.*, 1951, 1955). The much larger number of patients in the present review permits a fuller statistical analysis of some of the factors influencing the final result.

Selection of Patients

The criteria for the choice of patients for ^{131}I therapy have remained constant throughout the period of study. The following groups have been considered suitable. (1) Patients over 45 years of age. (2) Younger patients in whom there is associated disease, particularly cardiovascular complications, probably reducing the life expectancy to less than 20 years. (3) Patients who have relapsed following thyroidectomy. (4) Patients who have not remained euthyroid following a course of treatment with antithyroid drugs or have shown toxic reactions to these drugs and who are considered unsuitable for or have refused partial thyroidectomy.

Pregnancy is a complete contraindication for this form of treatment. The presence of tracheal deviation or compression associated with thyroid enlargement is not now regarded as a contraindication to ^{131}I therapy. Cases with this complication are described below.

Methods of Treatment

Dose of ^{131}I

The intention has been to deliver a dose to the thyroid in the region of 7,000 rads in the average uncomplicated case of thyrotoxicosis. A slightly greater dose has been chosen for patients with severe hyperthyroidism, nodular glands, or disabling cardiac complications. It has been thought advisable to give slightly smaller doses in the treatment of post-operative recurrences and milder cases with small smooth glands. However, in practice, accurate prediction of the dose is difficult and great accuracy cannot be achieved in delivering the prescribed dose.

The calculation of the number of millicuries of ^{131}I to be given to the patient to provide the intended rad dose to the thyroid depends on the size of the gland and the proportion of the dose taken up by and retained in the gland. The following formula, described in the earlier report (Blomfield *et al.*, 1955), has been used:

$$\text{Expected rads/mc.} = \frac{820 \times \text{48-hour \% uptake in preliminary tracer study}}{\text{Estimated gland weight in g.}}$$

In all cases a preliminary tracer test with ^{131}I was carried out shortly before ^{131}I therapy, and the uptake at 48 hours was measured as a forecast of the anticipated uptake of the therapy dose.

In estimating the gland weight, which is an obvious source of error, we have relied principally on palpation by several experienced observers, and the mean estimate of mass has been taken for the purpose of treatment. An attempt has been made to measure the size of the thyroid by counting antero-posteriorly and laterally

with a heavily collimated instrument (Blomfield *et al.*, 1953). In 21 experiments estimates of the size of various containers resembling in shape the thyroid gland and placed in a model neck were made with a scintillation counter. The volume of the active material was known accurately. In the small models up to 50 ml. the method gave an overestimate by as much as 50% or more. Above 50 ml. the scintillation method was accurate within the range of ±25%.

The actual irradiation dose received by the thyroid gland has been estimated retrospectively by daily measurements of the ^{131}I content of the thyroid gland over the ensuing eight days.

The following formula has been employed:

$$\text{Dose in rads} = \frac{164 \times T \times U \times M}{W}$$

where T is the effective half-life of the isotope in the thyroid, U the estimated peak percentage uptake of the therapy dose, M the dose in millicuries, and W the estimated thyroid mass in grammes.

Follow-up of Treated Cases.—The patients were seen at the thyroid clinic monthly for two months after therapy and thereafter at increasing intervals, provided satisfactory progress was made. The final assessment was made on clinical grounds, but in all cases of doubt confirmation was sought from further ^{131}I tracer tests and measurements of basal metabolic rate and serum cholesterol.

Repetition of ^{131}I Therapy.—A further therapeutic dose of ^{131}I was not given until at least three months had elapsed after the first dose. So long as any improvement was occurring a repetition of treatment was not considered. Persistent hyperthyroidism which remained stationary or became more severe after that interval indicated the need for further treatment with ^{131}I. The second dose was calculated on the same general principles as the first, but as some improvement had almost invariably taken place a slightly lower dose in the region of 5,000 to 7,000 rads was usually planned on a second or later occasion.

Results

The results of the treatment of thyrotoxicosis with ^{131}I in 500 patients since January, 1949, are shown in Table I. There are 398 women and 102 men, giving a female : male ratio of almost 4 : 1. The mean age of the group is 50.9 years, the distribution being shown in Fig. 1. The last patient first reported for treatment in February, 1957, and the results are based on a review completed in March, 1958. At that time in the whole group 80% had become euthyroid and 12% permanently hypothyroid; 2% were still hyperthyroid in varying degree, 4% had died before final assessment was possible, and 2% could not be traced.

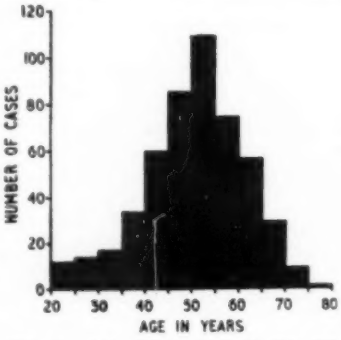


FIG. 1.—Age distribution of the 500 treated cases at the time of the first treatment.

The patients have been grouped on the basis of the clinical features presented by the thyroid gland. All post-operative recurrences of thyrotoxicosis have been considered separately, even though nodularity or diffuse enlargement developed after the operation. The remainder have been divided into three groups—namely, those showing no abnormality, those showing diffuse enlargement, and those with nodularity. No attempt has been made to place the solitary nodule or adenoma in a special category, as often this clinical finding is not confirmed by later pathological examination, which reveals many smaller nodules impalpable in life (Mortensen *et al.*, 1955). In all patients with thyroid enlargement, whether diffuse or nodular, definite shrinkage occurred after treatment. This ensured a good cosmetic result in all patients even though gross enlargement was present initially (Fig. 2). Improvement in exophthalmos and lid retraction was also the rule in the overwhelming majority of cases.

Euthyroid Patients

The proportion becoming euthyroid after a single dose is similar in all clinical groups and is in the narrow range 57–60%. In this group without palpable abnormality in the thyroid fewer required a second treatment and more became hypothyroid.

TABLE I.—*Results of Treatment with ^{131}I. Minimum Follow-up, One Year*

Clinical Group	Total in Group	% of Total	Euthyroid			Hypothyroid			Died before Euthyroid, still Hyperthyroid or Untraced			Age (Mean ± S.E.) (years)	Mean of First Dose (mc. ± S.E.)	Mean Irradiation to Thyroid from First Dose (Kilorads ± S.E.)
			One Dose	Two or More Doses	Total	One Dose	Two or More Doses	Total	One Dose	Two or More Doses	Total			
Impalpable gland or no recorded abnormality	85	17·0	50	11	61	12	3	15	5	4	9	53·1 ±0·98	6·9 ±0·34	6·8 ±0·23
Percentage of group			(59)	(13)	(71·8)	(14)	(4)	(17·6)	(6)	(5)	(10·6)			
Diffuse enlargement	192	38·4	116	46	162	16	3	19	4	7	11	48·4 ±0·74	8·6 ±0·33	7·0 ±0·17
Percentage of group			(60)	(24)	(84·4)	(8)	(2)	(9·9)	(2)	(4)	(5·7)			
Nodular enlargement	162	32·4	93	34	127	14	2	16	11	8	19	54·6 ±0·76	9·2 ±0·36	7·3 ±0·17
Percentage of group			(57)	(21)	(78·4)	(9)	(1)	(9·9)	(7)	(5)	(11·7)			
Post-operative	61	12·2	36	13	49	7	3	10	1	1	2	43·2 ±1·30	7·2 ±0·57	6·4 ±0·30
Percentage of group			(59)	(21)	(80·3)	(11)	(5)	(16·4)	(2)	(2)	(3·3)			
Total	500	100	295	104	399	49	11	60	21	20	41	50·9 ±0·48	8·3 ±0·20	7·0 ±0·10
Percentage of group			(59)	(21)	(79·8)	(10)	(2)	(12·0)	(4)	(4)	(8·2)			

The rate of response to treatment is important (Fig. 3). Out of the 295 patients requiring only a single dose, 227 (77% of the total) became euthyroid within six months and a further 52 (18%) within 12 months. Nine, who eventually became euthyroid, were unplaced owing to erratic attendance for assessment. Of the 104 patients who required two or more doses, 77 required two doses, 20 three doses, 6 four doses, and 1 five doses. This last patient was particularly resistant to therapy, and she had previously been treated by partial thyroidectomy and methylthiouracil. The details are as follows.

Case 1: Gross Resistance to ^{131}I Therapy.—A girl, first seen at the age of 19, complained of progressive enlargement of the thyroid and of features typical of hyperthyroidism. Partial thyroidectomy was performed, with improvement. Within six months, however, her symptoms returned. Methylthiouracil therapy was begun, but, despite continuous treatment for a year, she failed to gain weight and remained hyperthyroid. At this time her pulse was 132 a minute, sleeping pulse 90/min.; B.M.R. +50%; the thyroid was grossly enlarged. *X*-ray examination of the thoracic inlet showed considerable tracheal narrowing; radioactive iodine uptake studies confirmed a marked degree of thyrotoxicosis (4-hour uptake 76%, 48-hour uptake 50%, 48-hour plasma 3.22% per litre, 48-hour protein-bound ^{131}I 2.67% per litre).

FIG. 2.—Clinical result of radio-iodine therapy. Left: Before treatment. Right: After treatment, showing shrinkage of gland and improvement of exophthalmos.

Although she was only 22 years of age at this time, it was decided to treat her with radioactive iodine in view of the severity of her condition and her resistance to other forms of treatment. She was given 11.2 mc. of ^{131}I, delivering 6,600 rads to the gland. She remained grossly hyperthyroid, and three months later a further 28.8 mc. (7,000 rads) was given. The improvement was only slight, and four months after this second dose another 18.0 mc. (4,000 rads) was given.

She then began to improve, but two further doses were required at eight months and 16 months after the third treatment (8.5 mc. (9,400 rads) and 4.2 mc. (6,200 rads) respectively). In all, she had received 70.7 mc. (33,200 rads) in five doses over a period of two years. When euthyroid, her gland, which was grossly enlarged before receiving ^{131}I, was no longer palpable and there was no evidence of tracheal compression.

Four years later she had a full-term normal delivery of a female child, who at the time of writing was 8 months old and entirely well.

Twenty-seven patients relapsed after an apparently successful first treatment. They had been considered euthyroid within six months of the administration of the therapy dose, but a few months later were again clearly hyperthyroid. Twenty-one became euthyroid after further doses and have remained so, two have become hypothyroid after a second dose, and four are still hyperthyroid, having recently been re-treated. None relapsed at a longer interval than one year after treatment.

Improvement may continue for many months after administration of a therapeutic dose of ^{131}I. The following case illustrates the importance of delaying re-treatment, even in patients with clinical and laboratory evidence of continuing hyperthyroidism, so long as there is any sign of improvement still occurring.

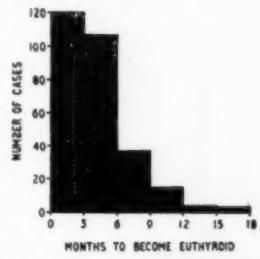


FIG. 3.—Time taken to become euthyroid following a single therapeutic dose of ^{131}I.

Case 2: Late Euthyroidism with a Single Dose.—A woman aged 65 had been treated for four years with intermittent courses of methylthiouracil with some improvement, but had never become completely euthyroid. Her main complaints were of swelling of the neck, loss of weight, and palpitations. On examination her pulse rate was 102/min., regular; her hands were hot and moist, with a fine tremor; the thyroid was enlarged (85 g.) and nodular; and a bruit was heard. There were no abnormal eye signs. She weighed 46.8 kg. (103 lb.) and the radioactive iodine tracer study was as follows: 4-hour uptake 55%, 48-hour uptake 57%, 48-hour plasma level 1.98% per litre, 48-hour P.B. ^{131}I 1.52% per litre. She was treated with ^{131}I (15.5 mc., 6,000 rads), but the response was slight.

Six months after therapy she weighed 46.4 kg. (102 lb.) and was still clinically thyrotoxic; pulse 120/min.; hands warm and moist, with a marked tremor; thyroid only just palpable. A repeat diagnostic tracer confirmed continuing hyperthyroidism (4-hour uptake 71.5%, 48-hour uptake 57.8%, 48-hour plasma 3.15% per litre, 48-hour P.B. ^{131}I 3.01% per litre).

She was requested to attend for further treatment, but failed to report and was not seen for a year. She attended again 18 months after therapy; her weight was then 52.7 kg. (116 lb.), pulse 100/min., and she was clinically mildly hyperthyroid. Repeat tracer study confirmed this (4-hour uptake 43.1%, 48-hour uptake 54.8%, plasma 1.34% per litre, P.B. ^{131}I 1.2% per litre). In view of her gain in weight it was decided to delay re-treatment, and on further review four months later her weight had risen to 55.9 kg. (123 lb.) and she was euthyroid; the pulse was 78 and regular, and she felt quite well. Six months later she had remained euthyroid.

The most valuable index to progress is a regular weight chart. If the weight is rising or steady the patient will often become euthyroid without further therapy. Although attention has been drawn to some cases in which the return to health was delayed it should be emphasized that in the majority this is achieved within four to six months. Furthermore, even in those not finally becoming euthyroid with one treatment some improvement always results and is noticeable within three or four weeks.

Hypothyroid Patients

The greatest incidence of hypothyroidism was seen in the group without palpable abnormality of the thyroid

gland. It was also above the average in the post-operative group. The patients with diffusely enlarged or nodular thyroids were apparently less liable to develop this complication ($P<0.05$). Hypothyroidism is usually manifest within six months of treatment (Fig. 4), but occasional cases have continued to appear. So far the longest interval has been 5½ years after therapy. In assessing results it is important to recognize this occasional late development of hypothyroidism. The following illustrative case is presented.

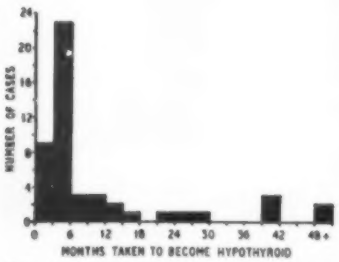


FIG. 4.—Time taken to become hypothyroid following a single therapeutic dose of ^{131}I.

Case 3: Late Myxoedema with a Small ^{131}I Dose. — A 23-year-old woman noticed prominence of her eyes and progressive enlargement of her neck; she complained of palpitations, excessive sweating, dyspnoea on exertion, nervousness, and irritability. On examination she had hot, moist skin; pulse rate 108/min. and regular; a diffusely enlarged thyroid; exophthalmos, lid retraction, and lid lag. She was treated with methylthiouracil for one year, but failed to improve, and partial thyroidectomy was carried out.

After the operation she remained well for six years, but at the age of 30 her symptoms recurred and she began to lose weight. On examination at this time she was obviously thyrotoxic and the thyroid was diffusely enlarged (estimated at 50 g.). Radio-iodine uptake study confirmed the diagnosis (uptake at 4 hours 65%, 48-hours 40.0%, 48-hour plasma activity 4.9% per litre, P.B. ^{131}I 3.8% per litre).

She was treated with ^{131}I, being given 7.8 mc., intended to deliver 6,000 rads to the gland. Retrospective estimation, however, revealed an actual dosage of only 2,500 rads due to an unduly short half-life of the isotope in the gland (1.4 days). The uptakes of the therapy dose agreed reasonably well with those of the tracer dose, being 62.5% at peak and 30% at 48 hours.

Despite the low radiation dosage received by the gland, she responded well, and eight months after treatment was considered euthyroid. Eighteen months after treatment she had a miscarriage, which may have been an early indication of a mild degree of hypothyroidism (King and Herring, 1939), although she was clinically euthyroid.

She was seen at regular intervals at the follow-up clinic, and three years after her radio-iodine therapy she complained of feeling cold and tired, of difficulty in remembering everyday events, and of a dry skin.

On examination her voice was gruff, the skin cold, dry, and scaly, the hair thin, and facies hypothyroid. Investigations showed: B.M.R. −23; serum cholesterol, 400 mg. per 100 ml.; E.C.G., low voltage with flattened T waves in all leads; 4-hour uptake of radio-iodine 4.0%, 48-hour uptake 4.7%.

She responded well to treatment with L-thyroxine sodium.

Hypothyroidism appearing within a few months of therapy may be transient. Several patients appear to pass through a hypothyroid phase in the period of two to three months after administration of ^{131}I and then recover spontaneously. The following patient illustrates this sequence of events.

Case 4: Temporary Myxoedema Following ^{131}I Therapy. —A man aged 57 complained of protrusion of the eyes for 10 months, associated with nervousness, excessive sweating, loss of weight, and palpitations. On examination his skin was warm and moist and there was a fine tremor of the outstretched hands. He had conspicuous exophthalmos and lid retraction. The thyroid gland was diffusely enlarged (estimated at 65 g.). He weighed 63.6 kg. (140 lb.).

A radioactive iodine diagnostic study was performed with the following results: uptake at 4 hours 83.5%, 48 hours 57.9%, 48-hour plasma activity 2.59% per litre, P.B. ^{131}I 2.34% per litre.

He was treated with 10 mc. of ^{131}I (6,000 rads) and improved rapidly, being euthyroid two months later—weight 74.1 kg. (163 lb.). In another month, however, he had developed a gruff voice, cold dry skin, and myxoedematous facies. He complained of feeling cold and of being slow in reaction and constipated. An E.C.G. showed low-voltage and flattened T waves in all leads; the serum cholesterol was 500 mg. per 100 ml. His weight had risen to 80 kg. (176 lb.).

Treatment was withheld and he slowly improved during the next six months, his E.C.G. reverting to normal and cholesterol falling to 320 mg. per 100 ml.

He has since been followed for another year, but has remained euthyroid, and his weight has stabilized at 75.9 kg. (167 lb.).

In view of the temporary nature of hypothyroidism in some patients, it is not our practice to institute treatment with thyroxine until observation has confirmed the permanent nature of the condition.

Factors Influencing the Response to ^{131}I Therapy

The intention is to restore health with a single therapeutic dose of ^{131}I, but in practice this has been achieved in only 59% of the patients. In the remaining 41% the reaction to the first dose has been either inadequate or excessive. Various factors that may influence the effect of a therapeutic dose of ^{131}I have been considered.

Age.—The response to the first therapeutic dose of ^{131}I in relation to the age of the patients has been studied. In the range between 20 and 80 years there is no evidence that there is any change in the sensitivity of the thyroid gland to irradiation.

Thyroid Gland Mass

The size of the thyroid is important in determining the dose of ^{131}I that is to be given. In the present work it has been estimated by palpation in all patients, and in 204 cases it has also been determined by scanning in two planes after a tracer dose. The palpation and scanning estimates differed by more than 20% in 80 patients, and in them the dose has been mainly based on the latter method. In the rest of the cases the palpation estimate only was available in deciding the therapy dose. An analysis of the response to the first treatment in relation to the estimated weight of the thyroid gland is shown in Table II. The percentage of patients still hyperthyroid after the first treatment rises with increasing gland mass and the proportion becoming hypothyroid falls. This relationship is statistically significant ($P<0.02$).

TABLE II.—*Relationship Between Clinical Result After First Treatment with ^{131}I and Estimated Gland Mass*

Gland Mass (g.)	Total No.	Euthyroid		Hypothyroid		Hyperthyroid	
		No.	%	No.	%	No.	%
<40	145	96	66·2	18	12·4	31	21·4
41–60	188	108	57·4	20	10·6	60	32·0
61–80	80	44	55·0	7	8·7	29	36·3
81–100	48	30	62·5	3	6·2	15	31·3
101+	39	17	43·5	1	2·6	21	54·0
Total	500	295	59·0	49	9·8	156	31·2

It is difficult to check the accuracy of the estimates of thyroid gland size obtained by palpation, but the results obtained by this method have been compared with those recorded by the physical method in the same patients (Fig. 5). The latter shows a much wider range, and in comparison palpation has overestimated the size of the smaller glands and underestimated the size of

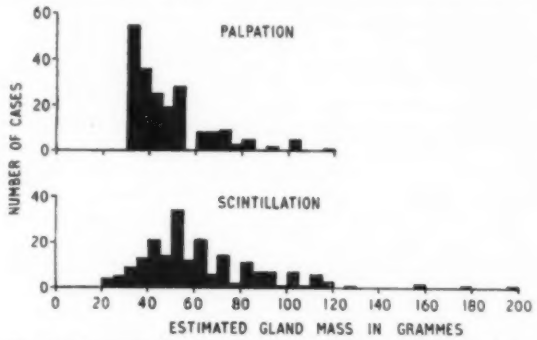


FIG. 5.—Comparison of the estimation of gland mass by palpation and by scintillation techniques.

the larger. In six patients dying within 10 weeks after the therapy dose the weight of the gland measured at necropsy is compared with the estimates made by palpation before treatment (Table III). If it is assumed

TABLE III.—*Comparison Between Palpation Estimates of Gland Mass and Necropsy Weights in Patients Dying Shortly After Therapy*

Patient	Necropsy Weight	Palpation Estimate	Interval Between Therapy and Death
G.B.	26 g.	50 g.	6 days
Z.D.	31 g.	40 g.	6 weeks
A.B.	40 g.	50 g.	10 ,,
O.H.	47 g.	40 g.	17 days
A.H.	130 g.	120 g.	4 ,,
I.G.	210 g.	115 g.	4 weeks

that the size of the gland does not change greatly within the relatively short period between therapy and death, it is again apparent in this series that on palpation the smaller glands have been overestimated in weight and the larger ones underestimated.

Thyroidal Uptake of ^{131}I

The therapy dose of ^{131}I is based on the uptake measured previously with a tracer dose of the isotope. The clinical result has been assessed in relation to this preliminary test (Table IV). In a small group the 48-hour uptake on the tracer test was low, below 40%, and in them the response to treatment was disappointing. The best results were seen in the group with an uptake in the 41–60% range, and there was a slight decline with the higher ranges of uptake.

In calculating the amount of ^{131}I required for treatment, the assumption is made that the uptakes of

TABLE IV.—*Relationship Between Clinical Result After First Treatment with ^{131}I and 48-hour Uptake of Tracer Dose*

*48-hour Uptake %	Total No.	Euthyroid		Hypothyroid		Hyperthyroid	
		No.	%	No.	%	No.	%
<40	28	12	42·9	1	3·6	15	53·6
41–60	165	103	62·4	15	9·1	47	28·5
61–80	269	158	58·7	30	11·1	81	30·2
80+	31	17	54·8	2	6·4	12	38·8

* Not known in seven cases.

the tracer and subsequent therapy doses will be similar. However, there is often a considerable discrepancy between the two measurements. In Fig. 6 the distribution is shown of the differences in these uptakes expressed as a percentage of the tracer uptake at 48 hours. The therapy uptakes on the average are lower than the tracer, and the mean depression of −5.0% is significant ($P<0.001$). The two sets of measurements were made on different counter systems in different laboratories. Cross-checks did not reveal any consistent errors, though some minor fluctuations in sensitivity may occasionally have arisen. However, there are many wide variations in both directions, which cannot be accounted for by physical errors in estimating uptake. Nevertheless, these differences were not associated with definite changes in the clinical results of treatment. An

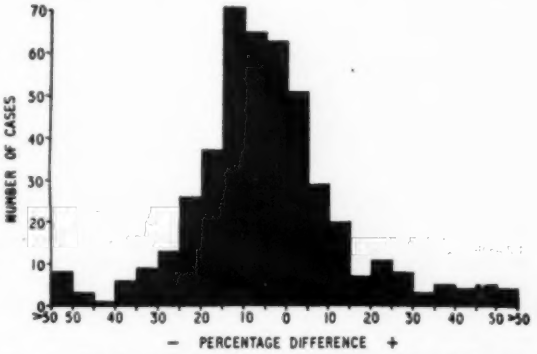


FIG. 6.—Distribution of difference between uptake of therapy dose at 48 hours and uptake of tracer dose at 48 hours as percentage of tracer uptake at 48 hours.

examination of 46 cases in which the discrepancy between the two tests lay outside the range ±12% did not show an increased incidence of hypothyroidism or of necessity for further treatment.

Biological Half-life of ^{131}I in Thyroid

The rate of decrease of radioactivity in the thyroid gland is extremely variable, but despite these considerable differences it is not related closely to the clinical result (Table V). In this group of 420 cases the mean biological half-life was 13.0 days ± 0.25 (S.E.).

TABLE V.—*Relationship Between Clinical Result After First Treatment with ^{131}I and the Biological Half-life of the Therapy Dose in 420 Cases*

*Biological Half-life in Days	Total No.	Euthyroid		Hypothyroid		Hyperthyroid	
		No.	%	No.	%	No.	%
0–5	75	45	60·0	6	8·0	24	32·0
5·1–10	142	83	58·4	17	12·0	42	29·6
10·1–15	86	51	59·3	8	9·3	27	31·4
15·1–20	45	29	64·4	4	8·9	12	26·7
20·1–25	32	19	59·4	5	15·6	8	25·0
25·1+	40	22	55·0	3	7·5	15	37·5

* In 80 cases the activity in the gland following treatment did not fall away in an exponential fashion. No half-life was therefore calculated.

Irradiation Dose.—The relationship between the amount of ^{131}I in millicuries given to the patient and the clinical result is shown in Table VI. Judging by the percentage becoming euthyroid with one treatment, there is an apparent decrease in response with the larger amounts. These, however, were given to the patients with the bigger glands, and, as previously noted, their mass was probably underestimated.

TABLE VI.—*Relationship Between Clinical Result After First Treatment with ^{131}I and Dose in Millicuries*

*Dose in mc.	Total No.	Euthyroid		Hypothyroid		Hyperthyroid	
		No.	%	No.	%	No.	%
<4	40	27	67·5	3	7·5	10	25·0
4·1–6	139	86	61·9	23	16·5	30	21·6
6·1–8	113	70	61·9	8	7·1	35	31·0
8·1–10	75	44	58·7	6	8·0	25	33·3
10·1–14	73	37	50·6	8	11·0	28	38·4
14·1+	59	30	50·8	1	1·7	28	47·5

* Record of dose in one patient not available.

TABLE VII.—*Relationship Between Clinical Result After First Treatment with ^{131}I and Irradiation to Thyroid in Kilorads*

*Dose to Thyroid in Kilorads	Total No.	Euthyroid		Hypothyroid		Hyperthyroid	
		No.	%	No.	%	No.	%
<4·0	39	19	48·7	4	10·3	16	41·0
4·1–6·0	120	75	62·5	11	9·2	34	28·3
6·1–8·0	191	117	61·3	13	6·8	61	31·9
8·1–10·0	117	66	56·4	16	13·7	35	29·9
10·1+	32	18	56·2	5	15·6	9	28·2

* Record of dose in one patient not available.

The dose to the thyroid gland was calculated retrospectively in kilorads on the basis of the estimated gland mass, estimated peak uptake, and effective half-life, as previously described (Table VII). A small group received a dose to the thyroid of under 4 kilorads, and this was largely due to an unexpectedly short effective half-life in the gland. As might be anticipated, the number becoming euthyroid with this treatment was reduced. However, it should be noted that even at this level 10% became hypothyroid. At the other end of the scale there was a small group receiving over 10 kilorads. This high dose was usually due to a longer effective half-life and higher uptake than was anticipated. The percentage becoming hypothyroid was slightly above the average. Nevertheless, the percentage requiring a second treatment still remained high.

Protein-bound ^{131}I

In a previous review of the first 140 patients in this series a possible correlation between the level of P.B. ^{131}I measured 48 hours after a tracer dose and the clinical result after a therapeutic dose was noted. This relationship has now been examined in the whole series of 500 patients, but has not been confirmed (Table VIII).

TABLE VIII.—*Relationship Between Clinical Result After First Treatment with ^{131}I and 48-hour P.B. ^{131}I from Tracer Dose*

*48-hour P.B.^{131}I	Total No.	Euthyroid		Hypothyroid		Hyperthyroid	
		No.	%	No.	%	No.	%
<0·5	35	19	54·2	5	14·3	11	31·4
0·5–0·99	134	91	67·9	14	10·4	29	21·6
1·0–1·49	145	84	57·9	17	11·7	44	30·3
1·5–1·99	64	33	51·5	6	9·4	25	39·1
2·0+	114	62	54·4	7	6·1	45	39·5

* Eight records not available owing to breakages in centrifuge.

Though there is a possible increase in persistent hyperthyroidism and a decrease in hypothyroidism with rising values of P.B. ^{131}I, this trend does not attain statistical significance.

Previous Treatment with Antithyroid Drugs

Thirty-nine patients had received methylthiouracil, propylthiouracil, or carbimazole within six months before the administration of the therapy dose, 16 of these having received the drug within a month of therapy. No iodide was given after stopping the treatment with antithyroid drugs, and the dose of ^{131}I was calculated in the same way as in the other cases. There was no definite evidence that the previous treatment influenced the response of the thyroid to irradiation. Twenty-one (54%) became euthyroid after a single dose of ^{131}I and six (15%) became hypothyroid. The numbers involved are small, and these results do not differ significantly from those recorded in the patients who had not received previous treatment with antithyroid drugs.

Factors Associated with Failure of First Dose of ^{131}I

The patients who developed hypothyroidism or required further treatment after the first administration of ^{131}I have been studied in relation to a combination of factors that may influence the actual dose to the thyroid gland. A greater dose than anticipated will be delivered to glands in which the therapy uptake exceeds the tracer uptake and in which the biological half-life is longer than usual. However, the majority of cases of hypothyroidism were not associated with these circumstances; conversely, persistent hypothyroidism was not more commonly associated with combined presence of a low uptake and a short biological half-life. Of all the factors that have been studied, the estimated gland mass has been the most important in relation to the clinical result.

Complications of Treatment

Exacerbation of Hyperthyroidism. — Although irradiation of the thyroid may lead to an increased release of iodinated compounds from the gland (Barker, 1955), transient exacerbation of thyrotoxic symptoms has been noted in only two patients. In none of the first 500 patients was any serious disturbance approaching a thyroid crisis observed, but subsequently we have seen one patient in whom a thyroid crisis occurred in the first week following 4.3 mc. of ^{131}I. In a few cases a transient aching in the neck has developed after therapy and persisted for a few days. This has never been severe and has caused only minimal discomfort. In the previous report (Blomfield *et al.*, 1955) two cases of urticaria and one of transient thrombocytopenia were noted, but no further cases have appeared.

Rheumatic Complaints.—Several patients have commented on transient rheumatic pains developing after treatment. These are commonly only mild and seldom require analgesics. A detailed analysis showed that 9% of patients attending at the follow-up clinics had complaints of this type. They probably do not represent a complication of treatment, as the incidence of rheumatic complaints in the general population is at about this level (Kellgren and Lawrence, 1956).

Associated Conditions

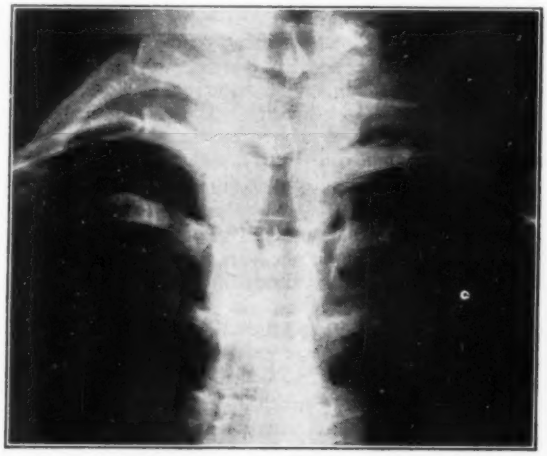
Tracheal Compression and Deviation.—In 78 patients there was definite radiological evidence of distortion of the trachea by an enlarged thyroid gland. The shrinkage of the gland after therapy was associated with a return of the tracheal anatomy to normal. Usually patients with severe tracheal compression have been treated surgically, but five with gross abnormalities in the trachea giving rise to symptoms have been treated with ^{131}I as they were extremely ill. The intention had been to refer them at a later stage for surgical relief of the tracheal distortion, but this was unnecessary, as contraction of the thyroid after radio-iodine therapy

entirely relieved the pressure on the trachea. The following two cases illustrate the relief of tracheal compression and tracheal distortion.

Case 5: Tracheal Compression.—A woman aged 23 complained of swelling of the neck of eight months' duration, associated with loss of weight, nervousness, irritability, excessive sweating, palpitations, and dyspnoea on exertion.

On examination she had warm, moist skin, with a marked tremor of the hands. The thyroid was diffusely enlarged, with a thrill palpable over it. There was conspicuous exophthalmos, lid retraction, and lag. She had early signs of congestive cardiac failure with slight ankle oedema and a raised jugular venous pressure. The B.M.R. estimation was +65% and *x*-ray examination of the thoracic inlet showed some tracheal narrowing.

Treatment was begun with carbimazole, 10 mg. three times daily, in an effort to improve her sufficiently for thyroidectomy. Two months later she was much improved, and, preparatory to surgery, the antithyroid drug was stopped and Lugol's iodine begun. However, her sleeping pulse rate remained high and she became rapidly more thyrotoxic, with a pulse rate of 150 and profuse sweating. She then developed stridor and the signs of a left lower lobe pneumonia. *X*-ray examination now showed the trachea to be narrowed and displaced anteriorly by an enlarged thyroid and confirmed left lower lobe consolidation.



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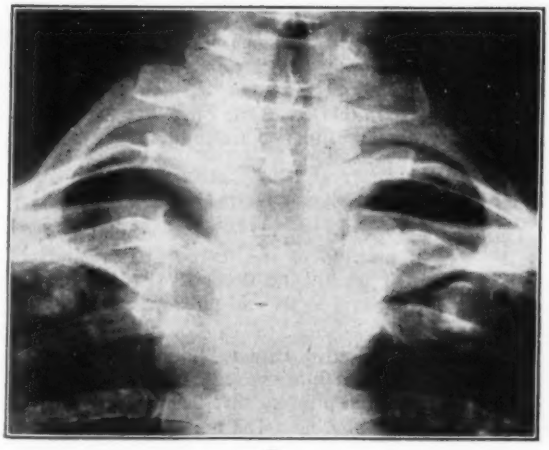

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FIG. 7.—Effect of radio-iodine therapy on tracheal compression. (A) Before therapy; (B) after therapy, showing restoration of the tracheal outline to normal.

On recovery from the pneumonia she was grossly thyrotoxic and her condition was regarded as too serious for operation to be considered. Treatment was instituted with carbimazole, 60 mg. daily, and L-thyroxine sodium, 0.2 mg. daily, in an attempt to prevent further enlargement of the gland. Despite this precaution, the gland size increased and the stridor became alarming. *X*-ray examination of the thoracic inlet showed the trachea to be considerably compressed just above the level of the clavicles (Fig. 7,A).

It was decided to treat her with radioactive iodine, and she was given 14 mc., which delivered 5,500 rads to a gland estimated as 200 g. in weight.

She improved following this, but four months later she was still hyperthyroid, and a further 20 mc. (5,500 rads) was given. She responded well to this second dose, but two and a half years later she required a final dose of 2.6 mc. (5,000 rads) to make her finally euthyroid.

At this time her gland was almost normal in size and her previously severe exophthalmos was considerably improved. A further *x*-ray examination showed the trachea to be midline with no visible compression (Fig. 7,B).

Case 6: Tracheal Compression and Deviation.—A 66-year-old woman complained of loss of weight, excessive sweating, palpitations, and swelling of the neck of six months' duration. She was treated with methylthiouracil and improved greatly, being considered euthyroid 12 months after starting with the drug, which was continued for another six months and then stopped.

She remained well for three years, when she again noticed loss of weight, excessive sweating, and palpitations. At the same time her goitre enlarged, causing a choking sensation, dyspnoea, and recurrent hoarseness.

On examination she was thin and hyperkinetic. There were no eye signs of thyrotoxicosis. Her hands were hot and moist, with a fine tremor. Pulse 90/min., regular; B.P. 190/90. The thyroid was firm and nodular, estimated at 100 g. There was a bruit over the larger left lobe. The trachea was deviated to the right. *X*-ray examination of the thoracic inlet confirmed marked tracheal deviation by an enlarged left lobe of thyroid (Fig. 8,A). A ^{131}I diagnostic tracer study was performed with the following results: 4-hour uptake 62%, 48-hour uptake 68%, plasma at 48 hours 0.22% per litre, 48-hour P.B. ^{131}I 0.18% per litre.

She was given 8.5 mc. of ^{131}I, delivering 7,400 rads to a 100-g. gland.

There was no increase in the tracheal compression symptoms, and she finally became euthyroid and asymptomatic four months after therapy. A follow-up *x*-ray examination of the thoracic inlet showed that the trachea had returned almost to the midline and was of normal configuration (Fig. 8,B).

Cardiac Abnormalities.—In 160 out of the 500 patients the thyrotoxicosis was complicated by the presence of cardiac complications. Congestive cardiac failure was present in 60 patients, and two-thirds of these, followed for periods of one to seven years after successful treatment of the thyrotoxicosis with ^{131}I, have remained free from further attacks of failure. Auricular fibrillation was observed in 90 patients before treatment and normal sinus rhythm was subsequently restored in 33. The nature and prognosis of the cardiac complications in these cases treated with ^{131}I are described in detail elsewhere (Sandler and Wilson, 1959).

Radioactivity in the Plasma and Pregnancy after ^{131}I Therapy

In thyrotoxic patients some of the administered ^{131}I is subsequently secreted as thyroid hormone. This results in a sustained high level of activity in the plasma and consequently in the irradiation of tissues distant

from the thyroid gland. The bone marrow and the gonads are of particular importance, the latter especially in the younger patients. The plasma dose was estimated for a group of 149 patients comprising women below the age of 45 and men below the age of 50. Plasma concentrations of ^{131}I were measured in all patients during the preliminary tracer test but in only a few after the therapy dose. However, on the occasions when both measurements were made, the proportion of the dose appearing in the plasma was approximately the same. The estimations were based mainly on the plasma activity at 48 hours in the tracer test, when the ^{131}I is largely protein-bound, but a small correction has been made for the dose received before the initial clearance of inorganic ^{131}I by the thyroid gland. The effective half-life of the activity in the plasma has been taken as seven days. The dose is almost entirely due to β-rays, but a small contribution (10%) from γ-rays is included.

The mean plasma dose was 25 rads. The range was very wide, from 2 to 260 rads, the latter being the integrated dose to the patient with the highly resistant gland (Case 1). In most patients it was much less, but in a few of those receiving multiple treatments the dose was greatly in excess of the mean (Fig. 9). Although the number of millicuries of ^{131}I given in second and later treatments is usually less than on the first occasion, the plasma specific activity is invariably higher; in consequence the plasma dose with repeat treatment is at least as great as with the first. The plasma dose and the gonad dose must clearly be associated, but the precise relationship in thyrotoxic patients is not known.

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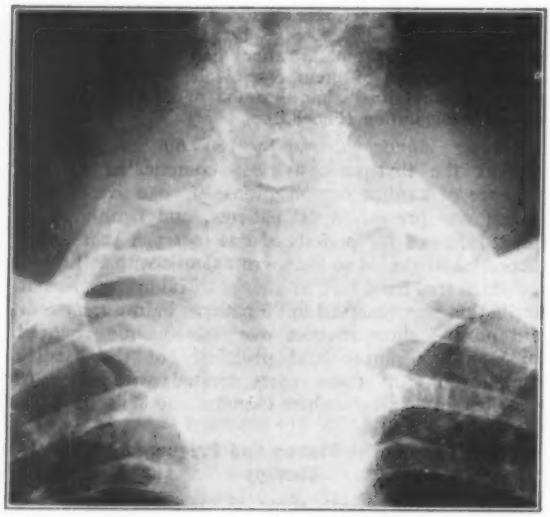

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FIG. 8.—Effect of radio-iodine therapy on tracheal deviation. (A) Before treatment. (B) After treatment, showing almost complete return of the trachea to the midline.

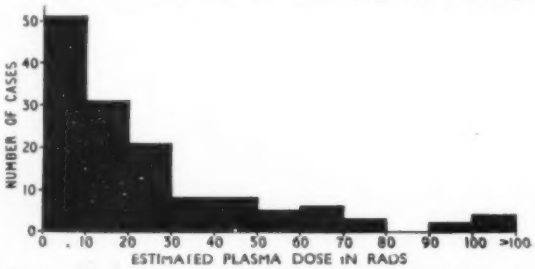

FIG. 9.—Estimated irradiation to the blood after ^{131}I therapy in women under the age of 45 and men under the age of 50.

Pregnancy is an absolute contraindication to the administration of ^{131}I. However, one patient was inadvertently treated about three weeks after conception. Another conceived about one week after the administration of a therapeutic dose of ^{131}I. Both these pregnancies were mentioned in the previous report (Blomfield *et al.*, 1955), and the children have developed normally over the past five years.

Nine other patients have conceived at intervals sufficiently long after treatment to ensure that the foetus was not exposed to any radiation from ^{131}I, and eight live children have been born. One patient conceived after becoming hypothyroid, but was treated with thyroxine and gave birth to a normal child. Three miscarriages have occurred, all in the first trimester, but there was no evidence to suggest that they were in any way associated with the previous treatment. One of these was placed between two normal pregnancies, all three being post-therapy. The other pregnancies in our series were uneventful, and the children have shown entirely normal progress.

Deaths After ^{131}I Therapy

Thirty patients out of the 500 in the series had died at the time of completion of the review. The interval between the first therapeutic dose of ^{131}I and death ranged from four days to six and three-quarter years.

In 18 death was due to cardiovascular disease presenting as congestive cardiac failure, myocardial infarction, or cerebral thrombosis. In four the cause was a carcinoma, the primary sites being in the breast, ovary, rectum, and thyroid. The breast carcinoma was present before ^{131}I was given. The deaths from carcinomas of the ovary and rectum occurred 13 months and 2½ years after ^{131}I therapy respectively. The patient with carcinoma of the thyroid died nine months after

treatment; the carcinoma was almost certainly present when the ^{131}I therapy was given, and the details have been reported elsewhere (Kilpatrick *et al.*, 1957). In the remaining eight patients death was predominantly due to respiratory infections. Five died within a month of receiving treatment; in three, death was due to congestive cardiac failure, in one to myocardial infarction, and in one to hyperparathyroidism. There was no evidence in any of these cases that death was precipitated by the administration of ^{131}I.

Among the 500 cases treated before March, 1957, and reviewed a year later, there were no deaths associated with leukaemia, and no cases of leukaemia or aplastic anaemia have arisen in this group. However, one case has arisen in a patient treated at a later date. She was a woman of 50, who received 4.9 mc. of ^{131}I in April, 1957. She became hypothyroid in October, 1957, and was subsequently treated with thyroxine. She died with acute leukaemia in September, 1958.

Post-mortem examinations were carried out in 13 patients. The thyroid glands were specially studied (Curran *et al.*, 1958). The chief features observed in the glands of patients dying within seven weeks of treatment were cell necrosis, disruption of follicles, oedema of the stroma, vascular damage, and a patchy distribution of ^{131}I. In the glands examined at longer intervals after therapy, bizarre cell forms, pyknotic nuclei, stromal fibrosis, capillary telangiectasia, and a relative absence of colloid were particularly noticeable.

In one patient dying within four days of the administration of 13.5 mc. of ^{131}I, a detailed study of the distribution of radioactivity was made in various organs. The results are shown in Table IX. In this case the dose to the testis was approximately two and a half times as great as the blood dose calculated as described above.

TABLE IX.—*Radiation Dosage Received by Individual Organs Measured at Necropsy. Man aged 52. Therapy*—13.5 *mc. Four Days Before Death*

Organ	Dose in Rads	Organ	Dose in Rads
Thyroid	8,300	Blood	42
Testis	103	Pancreas	37
Spleen	56	Bladder	29
Liver	44	Kidney	22
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Discussion

The advantages of ^{131}I treatment of thyrotoxicosis are readily seen. It is simple for the patient, effective, and devoid of any immediate serious complications. An ultimate permanent cure can be assured for all patients. The reaction to treatment is minimal and many can be treated on an out-patient basis. It is particularly suitable for those with cardiac complications. There are, however, some objections that can be raised to this form of treatment. They include a certain incidence of post-therapy hypothyroidism, delay in restoring euthyroidism in unduly resistant cases, the possible subsequent development of malignant disease, and undesirable genetic effects that might arise from exposure of the gonads to irradiation.

The problems of hypothyroidism and the necessity for repeated treatment in some cases are related to accurate assessment of the required dose. The incidence of hypothyroidism after partial thyroidectomy has varied from 2.9 to 13.9% (Bartels, 1953). The incidence reported after ^{131}I therapy also lies within this range, though on the average it is rather higher than commonly seen after surgical treatment. In the reported series of over 100 treated cases the incidence has varied from 2.5% (Gordon and Albright, 1950) to 17.2% (Clark and Rule, 1955). In the present state of knowledge accurate prediction of the correct dose cannot be ensured in all cases. The size of the thyroid is only one factor, but the results suggest that we have overestimated the mass of the smaller glands and thus tended to give too large doses at this end of the scale.

The minimum mass of the hyperactive thyroid has usually been regarded as 30 g., and our scale of estimates based on palpation has risen from this figure. However, in a series of 1,000 necropsies on euthyroid patients whose thyroids had been impalpable during life, Mortensen *et al.* (1955) noted that the largest number weighed between 15 and 35 g. Bauer and Blahd (1957) prepared scintigrams of 106 cases and report a range of gland sizes beginning at 15 g. The normal thyroid gland probably varies considerably in size in different parts of the world, and these American figures are not necessarily applicable to the Sheffield region. Nevertheless, the evidence obtained from our own scintillation studies and necropsy observations on hyperthyroid patients indicates that a lower figure for the impalpable thyroid would have been more appropriate. If this error had been avoided the incidence of hypothyroidism would have been slightly reduced but certainly not abolished. Accurate prediction in life of the mass of the thyroid is difficult, and a considerable error may be found in scintillation measurements when the estimates are compared with the actual weights of the glands (Kelly, 1954).

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It is important to note that myxoedema occasionally appears a year or longer after ^{131}I therapy and that an initially satisfactory result does not invariably ensure continuing euthyroidism. The reported incidence of hypothyroidism will increase with the duration of follow-up after therapy. On the other hand, recrudescence of hyperthyroidism after the patient has been euthyroid for a few months following ^{131}I therapy is rare, whereas after surgery there is usually a small recurrence rate. These differences in the behaviour of the hyperactive thyroid following surgery or ^{131}I therapy are consistent with the histological changes observed in the gland after the two methods of treatment (Curran *et al.*, 1958).

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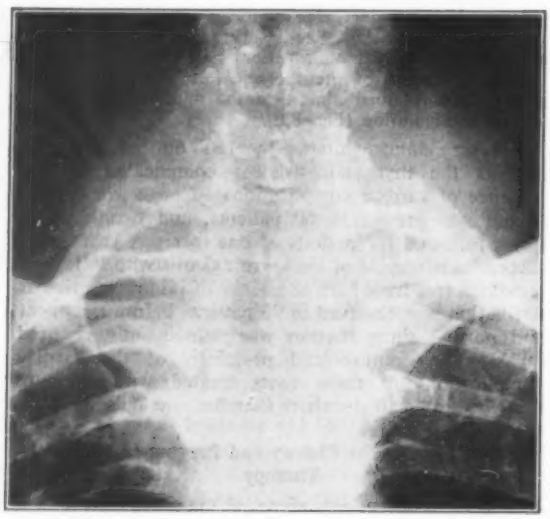

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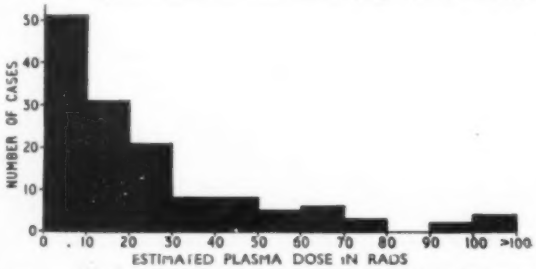

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It is important to note that myxoedema occasionally appears a year or longer after ^{131}I therapy and that an initially satisfactory result does not invariably ensure continuing euthyroidism. The reported incidence of hypothyroidism will increase with the duration of follow-up after therapy. On the other hand, recrudescence of hyperthyroidism after the patient has been euthyroid for a few months following ^{131}I therapy is rare, whereas after surgery there is usually a small recurrence rate. These differences in the behaviour of the hyperactive thyroid following surgery or ^{131}I therapy are consistent with the histological changes observed in the gland after the two methods of treatment (Curran *et al.*, 1958).

Relation Between Irradiation and Cancer

Much attention has been directed in recent years to the relation between exposure to ionizing radiation and the subsequent development of malignant disease, and it is clearly important to review ^{131}I therapy in the light of this work. Initially, the possibility of inducing a thyroid carcinoma many years after treatment received most consideration. Experimentally, thyroid carcinomas have been produced in rats by the administration of ^{131}I alone (Goldberg and Chaikoff, 1952), but in order to obtain a high incidence of cancer the employment of both goitrogens and ^{131}I has usually been necessary (Doniach, 1958). Maloof *et al.* (1952), using ^{131}I alone, found only one adenoma in the thyroids of 500 rats given doses of from 1 to 300 μc. There are now several reports of human thyroid cancers following irradiation of the neck region in childhood (Duffy and Fitzgerald, 1950; Simpson *et al.*, 1955; Clark, 1955; Simpson and Hempelmann, 1957; Kilpatrick *et al.*, 1957; Wilson *et al.*, 1958). In these patients the latent period has often been under 10 years, and the association must now be regarded as well established.

On the other hand, it is doubtful whether irradiation in adult life for the treatment of thyrotoxicosis predisposes to the development of a thyroid carcinoma (Quimby and Werner, 1949). In a survey of 100 patients with carcinoma of the thyroid, irradiation in adult life played no part in the pathogenesis of the disease (Kilpatrick *et al.*, 1957). Wilson *et al.* (1958) mention one patient, treated for thyrotoxicosis by *x*-ray therapy when she was 26 years old, who developed an anaplastic thyroid carcinoma 37 years later. Although many thousands of thyrotoxic patients have been treated with ^{131}I during the past 15 years no cases of carcinoma have yet been reported as a result of this therapy. If ^{131}I is carcinogenic in adults, the latent period is much longer than that observed following irradiation in childhood. The available evidence suggests that if ^{131}I therapy is restricted to adults the danger of the subsequent development of a carcinoma of the thyroid is remote.

Association with Leukaemia

The second possible radiation hazard is the subsequent development of leukaemia, and recent evidence suggests that this may possibly be more important than carcinoma of the thyroid. Leukaemia is a well-recognized consequence of irradiation (Medical Research Council, 1956), but it is still doubtful to what extent ^{131}I therapy may precipitate the development of this disease. Single cases of leukaemia have been described in patients treated for thyroid disorders by either external irradiation or large doses of ^{131}I (Delarue *et al.*, 1953; Seidlin *et al.*, 1954, 1955; Blom *et al.*, 1955; Rawson and Rall, 1955). Two cases of acute leukaemia have already been reported following the treatment of thyrotoxicosis with ^{131}I (Abbatt *et al.*, 1956; Pochin *et al.*, 1956), and we have now added a third. All three patients died within two years of a small dose, and the association may be fortuitous.

It seems probable that the dose to the bone marrow is of the same order as the blood dose. In adult patients developing leukaemia, after external irradiation employed in the treatment of ankylosing spondylitis, the dose to the spinal marrow in 2 out of 37 cases was 112 and 471 r (Court-Brown and Doll, 1957). In the remainder the dose varied between 500 and 2,000 r or more. These workers showed that under certain assumptions 30–50 r of irradiation with *x* rays to the whole marrow might be expected to double the incidence of leukaemia. The latent period for leukaemia after irradiation is usually about three to five years.

Genetic Effects

The effect of ionizing radiations on human genetics is at present ill understood, but they may increase the mutation rate, which "in a human population would have a relatively much greater effect upon the incidence of harmful than upon that of harmless or of advantageous hereditary traits" (Medical Research Council, 1956). This aspect is clearly of great importance in women who may later become pregnant and in men who are being treated with ^{131}I. The fraction of the dose received by the gonads after the administration of ^{131}I to euthyroid subjects is small, and in the studies of Kurland and Freedberg (1951) did not exceed 0.02% of the total amount given.

On the basis of this evidence it has been assumed by some that in thyrotoxic patients the exposure of the gonads will be less as a greater proportion of the dose is concentrated in the thyroid. However, after 24 hours P.B. ^{131}I is released from the gland in considerable quantity in thyrotoxic patients, and it is this fraction which is mainly responsible for the irradiation of the gonads. The measurement of the dose received by the testis in the thyrotoxic patient dying four days after the administration of ^{131}I, and the calculations made in other male patients and younger women, show that the gonads may receive an appreciable amount of irradiation. It is difficult to assess the significance of this exposure. The dose to the ovaries commonly given by *x* rays to induce an artificial menopause is approximately 400 r at a single occasion. However, there is no evidence to suggest that treatment with ^{131}I may lead to sterility, as the dose to the gonads is normally much below this level. The patient who received the largest plasma dose, 260 rads, became pregnant when euthyroid, and her child has developed normally. This dose was spread over five treatments during two years, however, and was therefore well below a sterilizing dose.

Apart from the possible direct effect on the patient, the contribution of ^{131}I therapy to the genetically significant irradiation exposure of the total population of the Sheffield region must be considered. About 270 cases of thyrotoxicosis are treated with ^{131}I in this region each year. The mean plasma dose to 149 younger cases (women under 45 and men under 50) was 25 rads. From the knowledge of the age and sex distribution of the treated patients under 50 years of age, the total genetically significant dose for our series of 500 cases was calculated. This was done by weighting the dose according to the risk of subsequent parenthood, as in the method used by Osborn and Smith (1956). The total genetically significant dose for these 500 cases was 1,526 rad-eg.* The annual genetically significant dose in the Sheffield region therefore due to this form of therapy might be expected to be approximately 824 rad-eg. In the 10 successful pregnancies occurring in our series the mean age of reproduction was 28.8 years $\pm$ 1.6 S.E. This suggests that the mean age of reproduction in these cases is not different from that of the general population.

*The rad equivalent genetic, or rad-eg, as used in this sense is radiation dose expressed in rads accumulated by the gonads of a person weighted according to the "risk of parenthood" taken from general population statistics.

The population of the region is 4.2×10^6 and the population of England and Wales is 44.9×10^6. Using the figures quoted by Osborn and Smith, the genetically significant natural background in the region would be about 0.28×10^6 rad-eg per year. The contribution of the ^{131}I therapy for thyrotoxicosis to the genetically significant dose is therefore approximately 0.3% of the natural background, as compared with the contribution made by diagnostic radiology estimated by Osborn and Smith as at least 22% of the natural background. Clearly, the contribution to any genetic hazard by the overall dose is small, provided that the basis of selection of patients for treatment remains unchanged.

Nodular Goitres

There has always been wide difference of opinion regarding the treatment of toxic nodular goitre. Patients with nodular enlargement constituted a large group in our series, but their response to ^{131}I therapy was just as satisfactory as that shown by the other groups. In treating patients with ^{131}I there is always the slight possibility that a carcinoma of the thyroid which is overlooked would have been revealed earlier by surgical operation. So far this has happened in only one of the 500 patients. Nodularity of the thyroid gland is extremely common in the older age groups (Schlesinger *et al.*, 1938). It is also important to appreciate that there is a conspicuous lack of correlation between the clinical assessment of thyroid nodularity and the pathological findings (Mortensen *et al.*, 1955). Furthermore, the majority of thyroid cancers probably do not arise in adenomatous goitres (Sloan, 1954). It is very doubtful whether nodularity of the thyrotoxic gland should be regarded as an indication for operation in the hope of discovering rather earlier a few cases of thyroid cancer. The basis for this opinion has been fully discussed elsewhere (Kilpatrick *et al.*, 1957).

Tracheal compression or deviation is often regarded as an indication for surgical treatment of thyrotoxicosis rather than for the administration of ^{131}I therapy. However, several patients in the present series with considerable tracheal abnormalities have responded well to treatment; the tracheal obstruction was not aggravated during the acute period after ^{131}I administration, and the compression and distortion were greatly relieved after a few months. Clearly ^{131}I therapy is not to be advocated for tracheal compression caused by calcified or fibrous glands or giving rise to symptoms for which urgent relief is required, but in suitable cases the final results are excellent.

Conclusion

From the point of view of the patient, ^{131}I is undoubtedly the most convenient form of treatment, as it involves no more than drinking a tasteless fluid, and admission to hospital is often not required. It does involve the availability of special equipment and the presence of specially trained personnel. The hesitation about its widespread adoption in all cases of thyrotoxicosis is largely based on the uncertainty regarding possible long-term undesirable effects. At the present time these are difficult to assess. If treatment is confined to adults the available evidence suggests that the danger of carcinoma of the thyroid developing is remote. ^{131}I therapy of thyrotoxicosis results in only a low exposure of the bone marrow to ionizing radiations, but in the present state of knowledge this cannot be dismissed as insignificant.

The latent period for the development of leukaemia following exposure to irradiation is considerably less than that commonly seen in carcinoma (Medical Research Council, 1956). It is clearly most important that this aspect should be kept under careful review. Genetic considerations do not apply to women over 45 years of age, but in males and younger women this must not be overlooked. These points confirm our previously expressed view that ^{131}I therapy should not be given to patients under 40 years of age unless other methods of treatment have failed or cannot safely be employed. For these older patients the accumulated evidence confirms that it is a most satisfactory form of treatment.

Summary

The results of the treatment of 500 thyrotoxic patients with ^{131}I during the period January, 1949, to February, 1957, were reviewed in March, 1958.

After the first treatment 59% became euthyroid and 10% hypothyroid. A further 21% became euthyroid after two or more treatments. The overall incidence of hypothyroidism was 12%.

Factors influencing the response to treatment have been investigated. The gland size was the most important, but this was difficult to determine accurately. The highest incidence of hypothyroidism occurred in the patients with small glands, the size of which was probably overestimated. The age of the patient and wide variations in uptake and half-life of ^{131}I in the thyroid did not have any consistent effect on the clinical result.

Patients with tracheal compression or distortion due to thyroid enlargement were treated. No symptoms due to tracheal compression occurred after therapy, and the subsequent shrinkage of the gland restored the tracheal abnormality towards normal.

The irradiation dose to the plasma has been calculated for the younger patients. The mean plasma dose was 25 rads, but this was greatly exceeded in a few of the patients receiving two or more treatments.

Several normal pregnancies have occurred following therapy. Thirty patients have died, and the causes of death have been investigated.

Though ^{131}I therapy is effective and safe, in the present state of knowledge it should be given to patients under 40 years of age only when other methods of treatment have failed or cannot be employed. For older patients it is the method of choice.

We should like to thank many past and present members of the two departments who, at various times, have taken part in this work, and the physicians and surgeons who kindly referred patients for treatment. We are grateful to Mr. S. B. Osborn for his advice on the calculation of genetic hazards.

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Cerebral Palsy—Advances in Understanding and Care is published by the Association for the Aid of Crippled Children in New York (624 pages. Obtainable from Arthur F. Bird, 66, Chandos Place, London, W.C.2. Price 42s. 6d., plus postage 1s. 6d.). The author, Viola E. Cardwell, enlisted a team of expert advisers to help her in the preparation of the book, the primary objective of which "is to promote greater understanding, improved treatment, and more sympathetic guidance of the patient and his family who are faced with the multiplicity of the all but overwhelming problems engendered by cerebral palsy." The first part of the book is concerned with the medical aspects of cerebral palsy: aetiology, pathology, and diagnosis are all discussed in detail in the light of modern advances in neuroanatomy and neurophysiology. "The Individual with Cerebral Palsy and his Total Habilitation" is the heading of the second part, and here the author describes physical and psychological treatment and discusses the social and educational aspects of cerebral palsy so far as the individual is concerned. Finally, there is a section on community aspects of cerebral palsy, with chapters on research and prevention. This book gives a detailed account of how an advanced society is attempting by voluntary and municipal effort to meet the challenge which cerebral palsy presents to the medical and social services.

CANCER AND BRONCHITIS MORTALITY IN RELATION TO ATMOSPHERIC DEPOSIT AND SMOKE

BY

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Residents in large towns of England and Wales have always been subject to higher death rates than country dwellers, and much attention has been given to this in the Registrar-General's reports during the last century. Subdivision into sex, region, and social class does little to explain the urban excess; in 1930–2, for example, the standardized mortality figures for men aged 35–64 in unskilled and semi-skilled occupations showed urban/rural ratios of 134/80 in the north and 105/73 in the south and east outside Greater London, and for their wives the corresponding ratios were 128/104 and 103/92 (Registrar-General, 1938).

Two diseases for which the urban excess is very pronounced are bronchitis and lung cancer, and this is so in some regions for gastric cancer, whereas cancers of the intestine and breast show little relation to urbanization in Britain. The death rates from bronchitis and lung cancer are higher than in any other country, as is also the amount of air pollution from domestic chimneys; and in countries where coal is little used for domestic heating the urban excess is much smaller. In view of these facts atmospheric pollution of the kind found in British towns has been under suspicion as a causative agent both for bronchitis and for lung cancer, and I have suggested that pollution of food by exposure to dirty air might be a cause of the higher incidence of gastric cancer in towns. This paper records an attempt to obtain more conclusive evidence on these points by relating standardized mortality from bronchitis and cancers of four sites, with measurements of atmospheric deposit and suspended matter (smoke), in the county boroughs of England and Wales and in the administrative areas of Lancashire and the West Riding of Yorkshire, where such measurements have been made. Throughout the paper "S.M.R." (standardized mortality ratio) means 100 times the actual deaths of residents in the area divided by the number which would have occurred if the death rates at each age had been the same as the rates for England and Wales as a whole.

Previous Work

Bronchitis.—In the period 1950–3 the S.M.R. for males increased with degree of urbanization from 60 in rural districts to 133 in the conurbations, and for females from 69 to 129 (Registrar-General, 1956). The crude death rate per 100,000 in 1954 was 63 in all towns of England and Wales and 42 in rural areas, compared with only 5 to 7 in Copenhagen and rural parts of Denmark (Christensen and Wood, 1958), whilst the smoke concentration in Copenhagen was similar to that in a small urban district of Anglesey (Campbell and Clemmesen, 1956). In 10 subdivisions of London the S.M.R. of females in 1955 was correlated with smoke ($r=0.71$), but how much of this was due to variables such as length of residence in London and social class distribution remained in doubt (Gore and Shaddick, 1958).

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Lung Cancer.—In 1950–3 the S.M.R. for males increased with the degree of urbanization from 64 in rural districts to 126 in the conurbations, and for females it rose from 76 to 121 (Stocks, 1958b); in the towns it increased according to the number of inhabited dwellings (Stocks, 1952), and in rural districts it increased with population per acre (Curwen *et al.*, 1954). In the Liverpool and North Wales region death rates of male non-smokers and pipe smokers resident in urban Merseyside were twice as great as in the seaboard areas of Wales; for moderate cigarette smokers the ratio was 1.7, but for heavy cigarette smokers there was no urban excess (Stocks, 1958a). After correcting for differences in smoking habits urban residence appeared to add about 1 per 1,000 to the death rate at ages 35–74 in this region, compared with about one-fifth of that amount in the United States of America (Hammond and Horn, 1958). Smoke measurements at 15 places in the same region gave correlation coefficients of 0.83 both with lung cancer and population density in the districts around the instruments, and when population density was held constant the partial coefficients with lung cancer were 0.35 for total smoke concentration and 0.28 for 3:4-benzpyrene, 0.48 for 1:12-benzperylene, 0.19 for pyrene, and 0.13 for fluoranthene contents of the smoke particles, the number of localities being too small, however, to allow firm conclusions from these results (Stocks, 1958b).

Gastric Cancer.—In 1954 mortality at ages 35–74 was about 10% higher in large urban areas than in rural districts (Registrar-General, 1957). In 1949–51 the urban/rural ratio of incidence was about 1.3 in Connecticut and 1.15 in New York State, but in Scandinavian countries no appreciable urban excess has been found. A steady fall in death rates in the U.S.A. contrasts with unchanging rates in Britain (Haenszel, 1958). Relations with air pollution do not appear to have been investigated.

Intestinal Cancer.—In Connecticut and in New York and Iowa States the urban/rural ratios of incidence exceed 1.3 for males (Haenszel, 1958), but in the Liverpool and North Wales region no evidence was found of any relation between the incidence of cancers of the intestine and rectum and previous residence in an urban area (Stocks, 1958a). In the latter region there was no correlation between smoke concentrations at 15 places and mortality in the districts around the instruments (Stocks, 1958b).

Breast Cancer.—No statistical evidence for any influence of urbanization on incidence of this form of cancer has been found.

Method of Study

Four groups of places have been used in this study; (*a*) county boroughs throughout England and Wales having the necessary air-pollution data; (*b*) administrative areas within the boundaries of Lancashire and the West Riding of Yorkshire having the necessary data; (*c*) all urban districts in Lancashire; and (*d*) all administrative areas within the boundaries of Lancashire. Deaths from cancer of the lung and bronchus in the five years 1950–4, and from cancers of the stomach, intestine with rectum, and breast (females), and from bronchitis, in 1950–3* were obtained from the statistical reviews for each county borough, and from the county medical officers of health for each of the 198 administrative districts of the counties of Lancashire and the West Riding. Ratios of deaths in England and Wales in the same years to the census population at six age groups for each sex were multiplied by the corresponding local census populations, and the resulting products were aggregated to give the expected deaths, the S.M.R.s being 100 times the ratio of actual to expected deaths for males, females, or both sexes combined. The six age groups used for cancer were 0–34, 35–44, 45–54, 55–64, 65–74, and 75 and over; for bronchitis the first two groups were modified to 0–4 and 5–44.

The Department of Scientific and Industrial Research (1955) issued a report on "The Investigation of Atmospheric Pollution" during 10 years ending in March, 1954, and in Table 8 the average amounts were given of deposited matter in summer and winter per 100 square metres per month during the periods of years when deposit gauges were operating at over 250 stations, distinguishing total undissolved matter (subdivided into tar, ash, and other) and matter dissolved in the rain-water. Attention has been confined to the former total, using averages of the summer and winter figures for 1949–54 or the most recent period of years available, bringing in several towns where records have been obtained since the issue of the 10-year report. In most of the large towns multiple gauges were operating at different points, and in such cases those which had been sited intentionally close to special sources of pollution were not included —for example, in Sheffield an average for 15 sites was used after exclusion of 6, and in Middlesbrough 7 were used after excluding 3. Data were thus obtained from 207 gauges in respect of 53 county boroughs and from 174 gauges in the 74 Lancashire and West Riding areas.

Table 9 of the same report gives average concentrations of smoke per 100 cubic metres of air as determined by daily filters in 95 places, and, after excluding sites aimed at measuring special sources of pollution and adding a few places where smoke filters have been operating in Lancashire for the British Empire Cancer Campaign's survey, data were assembled for 58 localities. The average state of the air being inspired by the population of a large town cannot be measured accurately by observations made at a single point in it, but in choosing a site for a filter the aim was to sample the air at a point which appeared to be representative of the locality as a whole. Failure to achieve this aim in some places would lead to underestimation rather than exaggeration of the true correlation between mortality in a population and the state of the air to which it had been exposed. Another difficulty is the fact that pollution in some towns will have changed during the long period needed to produce the chronic disease under investigation, and measurements further back in time might be more appropriate. Despite these weaknesses, however, it was thought worth while to find whether or not correlations do exist between deposited matter and/or smoke and mortality from cancer and bronchitis in large towns and smaller areas, taking account of the population densities which could produce such correlations indirectly.

Results from County Boroughs

Table I shows the relevant data for 58 county boroughs with records of deposited matter or of smoke,

*The year 1954 was not included because of the change in General Register Office rules for allocating to place of residence deaths of persons in institutions for the chronic sick, which may have affected some local rates for these diseases, though not for lung cancer.

30 having the former only, 5 the latter only, and 23 having both. The first 53 are ranked in order of the "deposit index" or monthly average number of grammes of undissolved matter deposited per 100 square metres of surface. The "smoke index" is determined by drawing a measured volume of air continuously through a white filter-paper which is changed daily, and the darkness of the stain is matched with a standard scale and expressed in milligrams per 100 cubic metres of air and averaged throughout the period of years. The population density per acre is that in 1951, and the "social class index" is the number of men in class IV and V occupations per 100 of those in all occupations as given in Table XCVII of the *Statistical Review for 1934* (Registrar-General, 1936).

TABLE II

		Persons per Acre	Lung	Cancer S.M.R.			
				Stomach		Intestine	Breast
			P	M	F	P	F
Means	All 83 ..	15·42	104·8	111·4	106·2	104·1	96·8
	53 (deposit)	16·40	107·8	112·1	112·0	105·4	96·1
	28 (smoke)	18·00	113·1	118·2	109·3	108·7	98·4
Standard errors	53 ..	0·93	2·76	2·74	2·71	1·31	2·09
	28 ..	1·10	4·40	3·49	3·35	1·64	2·10

The figures for the various diseases are the S.M.R.s for males, females, or both sexes together (as indicated by "P").

Since there are 83 county boroughs, of which 25 had no pollution records, the mean values of the cancer and density indices are compared in Table II with those of the 53 and 28 used for correlation with deposit and smoke. With regard to the standard errors, the 53 towns with deposit data could be a random sample of the 83, but the 28 with smoke records have a larger mean population density and rather higher S.M.R.s, though the differences for the latter do not exceed twice the standard errors. Selectivity of the groups is not, therefore, serious. Table III shows that atmospheric deposit within the large towns is correlated with population density to the extent of r=0.219, a surprisingly low value, and between smoke and population density the relation is even slighter (r=0.061). Density per acre is influenced by the extension of boundaries beyond the suburbs, and Table I shows that towns such as Rotherham, St. Helens, Nottingham, Halifax, and Rochdale have densities below 10.

TABLE I.—*Air Pollution, Population Density, and Standardized Mortality in 58 County Boroughs of England and Wales*

County Borough	Deposit Index*	Smoke Index†	Persons per Acre	Bronchitis 1950–3		Lung Cancer P 1950–4	Cancer (1950–3) of			
				M	F		Stomach M	Stomach F	Intestine P	Breast F
Exeter	96	8	8·3	77	72	78	104	88	100	104
Southport	128		8·7	79	76	109	109	85	107	82
Newport	166		14·3	119	103	112	100	88	97	89
Gloucester	199		12·8	91	82	78	118	88	109	78
Great Yarmouth	200		14·2	86	95	94	67	84	110	151
Southampton	204	11	19·4	87	83	115	101	108	113	99
Darlington	231		13·1	93	121	78	118	120	112	104
Plymouth	239		15·9	73	84	84	106	115	90	87
Kingston-on-Hull	253	31	21·2	139	126	134	112	120	98	89
Wallasey	258		17·1	89	85	108	103	85	100	99
Bradford	268	33	11·4	147	120	104	112	103	113	118
Ipswich	275		11·9	74	81	93	87	95	90	122
Halifax	293		6·9	120	112	97	140	139	120	108
Doncaster	300		9·8	116	115	99	104	85	112	101
Preston	306	24	20·9	125	151	101	128	95	105	115
York	318		16·4	95	75	94	113	102	104	92
Bristol	320	7	16·8	82	90	113	83	95	94	99
Wolverhampton	326	6	17·8	128	110	88	104	100	116	99
South Shields	328		21·9	144	155	128	149	161	95	105
Smethwick	332		30·6	145	128	126	92	93	114	99
Wakefield	359		10·4	147	149	80	105	121	90	65
Walsall	360	25	13·0	140	104	106	106	87	112	112
Cardiff	361	8	16·2	126	98	110	132	111	94	107
Rochdale	364		9·2	126	145	70	134	137	111	96
Stockport	367		17·8	170	180	119	117	128	108	108
Bury	368		7·9	138	140	93	116	107	92	89
Coventry	368		13·5	86	111	96	88	96	98	89
Rotherham	384		8·9	138	134	93	139	131	113	104
West Bromwich	391		12·3	167	127	106	101	114	100	116
Stoke-on-Trent	402	44	13·0	161	168	130	159	150	119	87
Dewsbury	411		7·9	132	158	93	110	143	123	103
Grimsby	414		17·3	97	89	109	93	84	114	73
St. Helens	415	40	13·9	160	141	111	125	109	94	78
Oldham	419		22·7	200	268	94	149	141	114	97
Derby	423		17·4	88	74	89	107	88	92	91
Croydon	424		19·7	106	93	107	77	101	87	103
Huddersfield	434		9·1	107	123	82	95	117	111	96
Leicester	436	19	16·8	99	110	99	83	99	113	110
Nottingham	445	10	9·0	156	137	117	104	92	102	108
Sheffield	446	34	12·9	116	109	118	109	113	103	101
Newcastle upon Tyne	447	20	26·3	114	113	123	127	120	109	77
Liverpool	453	40	28·9	139	138	158	104	128	110	90
West Hartlepool	456		17·4	135	168	110	129	122	108	61
Bootle	483	42	13·1	194	164	146	123	122	106	86
Warrington	485	26	18·3	204	223	115	139	135	114	85
Manchester	488	26	25·8	185	187	150	131	119	115	100
Burnley	494	21	18·1	139	181	92	125	111	120	80
Gateshead	500		25·7	136	111	117	131	134	110	89
Bolton	505	32	10·9	140	176	97	141	129	122	97
Middlesbrough	528		20·7	126	83	123	121	129	112	78
Leeds	573	49	13·2	162	141	131	113	116	104	99
East Ham	704		36·4	131	123	132	127	109	93	104
Salford	731	36	34·2	259	240	159	168	129	120	97
Birmingham		24	21·7	135	137	131	106	106	120	135
Birkenhead		29	16·6	125	116	132	124	116	108	105
Chester		21	11·6	113	81	112	129	109	107	93
Oxford		14	11·7	81	59	116	98	65	90	112
Portsmouth		14	25·3	100	109	107	108	86	100	104

* Average amount of undissolved deposited matter in grammes per 100 square metres per month during 1949–54 or most recent period available.

† Average amount of suspended matter (smoke) in milligrams per 100 cubic metres of air during the most recent period available.

Relations with Deposit

Bronchitis is strongly correlated with amount of deposit, the coefficients for males (r=0.605) and females (r=0.537) being 4.4 and 3.9 times their standard errors. The partial coefficients when population density is held constant are 0.579 and 0.511 respectively. The regression of male bronchitis on deposit is 0.183—that is, the S.M.R. tends to rise by 18.3 for each gramme of deposit per square metre per month, and this is shown graphically in Fig 1 (a).

Lung cancer is related with density per acre (r=0.650), but hitherto it has remained uncertain how much of this is due to the greater air pollution arising from crowding of houses together and how much to other social factors, such as more cigarette-smoking and beer-drinking in congested areas. The correlation with amount of deposit (r=0.513) is 3.7 times its standard error, and a

partial coefficient of 0.500 remains when the population density is held constant, the odds against such a high value arising fortuitously being over 5,000 to 1. The regression is 0.0027—that is, an increase of 8.27 in the S.M.R. for each gramme per square metre per month, and Fig. 1 (b) shows that a straight line fits the distribution tolerably well. This undoubted association between lung cancer and deposit from the air does not account for the relation between lung cancer and population density, the partial coefficient when deposit is held constant being 0.60. Lung cancer is correlated with bronchitis in males when deposit is constant (r=0.309).

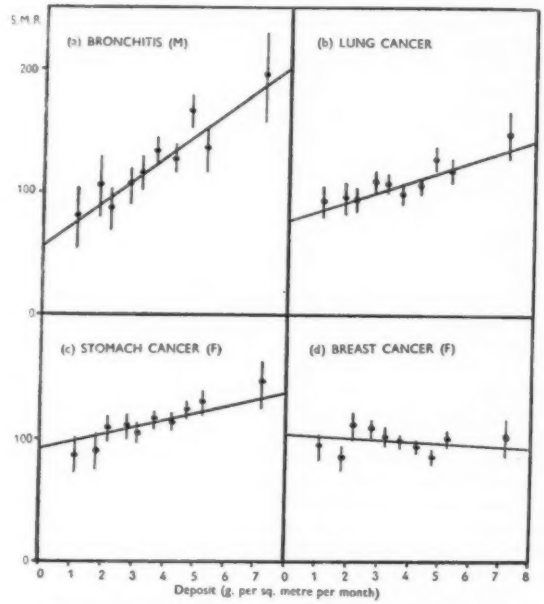
S.M.R.
(a) BRONCHITIS (M)
(b) LUNG CANCER
(c) STOMACH CANCER (F)
(d) BREAST CANCER (F)
200
100
0
0 1 2 3 4 5 6 7 0 1 2 3 4 5 6 7 8
Deposit (g. per sq. metre per month)

FIG. 1.—Bronchitis and cancer mortality in 53 county boroughs in relation to atmospheric deposit (undissolved). Mean S.M.R.s are denoted by dots, and the vertical lines through them indicate the standard errors above and below the mean. The equations of the regression lines of S.M.R. (m) on deposit (d) are: (*a*) m=61.3−0.183d, (*b*) m=76.5−0.0827d, (*c*) m=89.1−0.0605d, (*d*) m=103.3−0.0190d.

Stomach cancer also gives significant partial correlation coefficients with amount of deposit after eliminating population density—namely, 0.415 for males and 0.373 for females, with odds against these arising by chance of about 100 to 1. The regression line for females is shown in Fig. 1 (c). This form of cancer has a class gradient in towns, and the correlation with the social class index is 0.434. When this index is held constant the coefficient between stomach cancer and amount of deposit is 0.297, which exceeds twice its standard error. *Intestinal cancer* gives a partial coefficient of 0.186, which might arise by chance 1 in 6 times; and *breast cancer* gives an insignificant negative correlation, the regression being shown in Fig. 1 (d). The ratio of stomach to breast cancer S.M.R. increases regularly with the amount of deposit, as indicated in Table IV.

TABLE IV

Deposit Index:	50–	200–	250–	300–	350–	400–	450–	500+
Mean stomach S.M.R.	85	107	109	106	115	114	123	122
,, breast ,, ..	87·5	110	105	101	97	94	87	90
Ratio stomach/breast	0·97	0·97	1·04	1·05	1·19	1·31	1·41	1·35

Relations with Smoke

Bronchitis is correlated with smoke concentration in the same degree as with deposit, the partial coefficients after eliminating population density being 0.662 for males and 0.469 for females. *Lung cancer* gives a partial coefficient of 0.510, which is significant, the odds being over 100 to 1 against its occurrence by chance, and the regression of the S.M.R. on smoke is shown in Fig. 2 (a). *Stomach cancer* in males shows about the same degree of association with smoke as with deposit (r=0.440, P<0.05), and in females the coefficient is higher (r=0.620, P<0.001), whilst *breast cancer* gives a correspondingly high negative relation (r=0.384). The curious inverse association between stomach and breast

TABLE V

Smoke Index:	Under 15	15–29	30–39	40 and Over
Mean stomach S.M.R. ..	94	111	119	125
,, breast ,, ..	103	100	100	88
Ratio stomach/breast ..	0·9	1·1	1·2	1·4

TABLE III.—*Correlation Coefficients Between Mortality, Population Density, and Air Pollution Indices*

	With Population per Acre	With Standardized Mortality Ratio for: Bronchitis M	Bronchitis F	Lung Cancer P	Stomach Cancer M	Stomach Cancer F	Intestinal Cancer P	Breast Cancer F
				Atmospheric Deposit (Undissolved)				
County boroughs (53):								
Population density	—	0·346	*0·245*	0·650	*0·079*	*0·111*	*0·025*	*−0·095*
Deposit index	*0·219*	0·605	0·537	0·513	0·421	0·382	*0·184*	*−0·156*
,, ,, with density constant ..	—	0·579	0·511	0·500	0·415	0·373	*0·186*	*−0·135*
Lancs and Yorks (W. Riding) (74):								
Population density	—	0·458	0·334	0·625	*0·140*	*0·046*		*−0·017*
Deposit index	0·305	0·469	0·521	0·326	*0·211*	0·229		*0·039*
,, ,, with density constant ..	—	0·392	0·467	*0·182*	*0·179*	0·225		*0·035*
				Smoke (Suspended Matter)				
County boroughs (28):								
Population density	—	0·353	0·436	0·479	*0·185*	0·248	*0·239*	*−0·132*
Smoke index	*0·061*	0·640	0·448	0·474	0·443	0·617	*0·230*	−0·386
,, ,, with density constant ..	—	0·662	0·469	0·510	0·440	0·620	*0·222*	−0·384
Lancs and Yorks (W. Riding) (42):								
Population density	—	0·513	0·470	0·762	*0·160*	*−0·010*		*−0·034*
Smoke index	0·526	*0·299*	*0·198*	0·591	*0·208*	*0·200*		*0·015*
,, ,, with density constant ..	—	*0·040*	*−0·068*	0·345	*0·171*	*0·242*		*0·038*

Note.—Coefficients whose probability of fortuitous occurrence exceeds 1 in 20 are printed in italics.

in females is shown in Table V. *Intestinal cancer* shows a small positive correlation with smoke which is below the conventional level of significance.

Results from Lancashire and Yorkshire

Relations with Deposit.—In the 74 administrative areas with deposit gauges in Lancashire and the West Riding, the correlation between amount of deposit and density of population was 0.305. *Bronchitis* gives rather smaller correlations with deposit than in all county boroughs, but the partial coefficients when density is held constant are again highly significant (males 0.387 and females 0.467, respectively 3.1 and 3.8 times the standard errors). *Lung cancer* gives a coefficient of

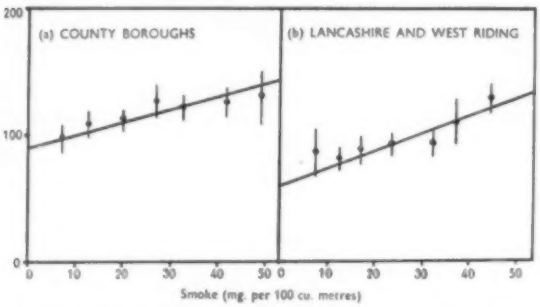

FIG. 2.—Lung cancer mortality in relation to smoke. Mean S.M.R.s are denoted by dots, and the vertical lines through them indicate the standard errors above and below the mean. The equations of the regression lines of S.M.R. (m) on smoke (s) are: (*a*) m=88.0+s. (*b*) m=59.2+1.47s.

0.326 with deposit, reduced to 0.182 with density constant. *Stomach cancer* gives partial coefficients of 0.179 for males and 0.225 for females, the latter being statistically significant (P=0.05). *Breast cancer* shows no relation with deposit.

Relations with Smoke.—In 42 areas of all kinds in this region, of which 31 were in Yorkshire and 11 in Lancashire, there were data available from smoke-measuring instruments, and the correlation between smoke and population density was 0.526. *Bronchitis* is not so strongly associated with smoke as with deposit in this region, and the partial coefficients fall to zero, in contrast with the high values for the county boroughs. *Lung cancer,* however, gives a first order correlation of 0.591, and the partial coefficient of 0.345 is above the conventional level of significance (P<0.05). The regression of the S.M.R. on smoke concentration is shown in Fig. 2 (b). *Stomach cancer* correlations with smoke are similar to those with deposit. *Breast cancer* shows no association with either population density or smoke.

Relation with Population Density in Adjacent Districts.—Death rates from bronchitis and stomach cancer have been shown to be related with smoke concentration in the larger towns, and lung cancer is so related in towns of all sizes and independently of the population density. Since some of the smoke in the air of a town has been brought by the wind from adjacent areas, the total smoke intensity must be a combined function of the number of chimneys in the town itself and in the districts surrounding. Lucas (1958) has shown that domestic chimneys contribute the major part of the sulphur dioxide pollution found near ground level, and has calculated the changes in its intensity as one passes from the windward edge across a town and then across the countryside to the lee of the town. From Fig. 6 (a) of this paper it appears that for a town six miles in diameter assumed to be surrounded by open country the total pollution near ground level spread over a six-mile stretch on the lee side of the town is approximately half of the total pollution affecting the town itself. Since the number of domestic chimneys is proportional to the population it may be deduced from this that the pollution intensity near ground level in a town of that size will be roughly proportional to the density of population in the town itself plus half the density in the districts surrounding the town. This assumes that "smoke" behaves in the same way as sulphur dioxide, that wind direction is fairly evenly distributed round the compass, and that its speed averages 5 feet per second. If lung cancer in a town is in fact affected by smoke in the air, it should be statistically related with the population density in the town itself, independently related with the average density in the districts surrounding the town, and more highly correlated with the first plus half the second of these densities than with either taken separately.

Table VI shows the results of applying this test to the 94 urban districts of Lancashire, and also to the 126 areas of all kinds in that county. In the 94 small towns the lung cancer correlations are 0.464 with population density in the town itself, 0.277 with the average density in the surrounding areas independently of the town, and 0.502 with density in the town plus half that in the surrounding areas, which was the result anticipated on the hypothesis that smoke is concerned in the causation

TABLE VI.—*Correlations Between Cancer Mortality in Lancashire and Population Density in the Same Area and Adjacent Districts*

	Sex	No. of Index Areas	Correlation with Population Density in						
			Index Area	Adjacent Districts to					Combined Areas*
				S.W.	S.E.	N.E.	N.W.	Mean	
Urban districts only:									
Density of population in index area		94	—					0·587	
Lung cancer S.M.R.	P	94	0·464					0·411	0·502
,, ,, with density in index area constant	P	94	—					0·277	
All types of area:									
Density of population in index area		126	—	0·291	0·394	0·384	0·466	0·525	
Lung cancer S.M.R.	P	126	0·573	0·235	0·356	0·410	0·360	0·464	0·603
Stomach cancer S.M.R.	M	126	0·196					*0·100*	
With index area density constant:									
Lung cancer	P	126	—	*0·087*	*0·174*	0·251	*0·147*	0·233	
Stomach ,,	M	126	—					*−0·004*	

* Correlation with sum of density in index area and half the mean density in adjacent districts (see text).
Note.—Coefficients whose probability of fortuitous occurrence exceeds 1 in 20 are printed in italics.

of lung cancer. That these relations could arise fortuitously is hardly credible, nor is any other explanation of them.

When the large towns and rural districts are included the correlation with density in the area itself is larger (0.573) and the partial coefficient with the average density in surrounding districts is smaller (0.233) than when only the small towns are considered, but there is a higher coefficient with population density in the area itself plus half that in surrounding districts (0.603). Differentiation of the adjacent districts into those abutting on four sectors of the boundary shows highest correlation with density of population to the north-east, and lowest with density to the south-west. It has to be remembered that the geography of Lancashire is peculiar, with the Pennine chain along its eastern side and the sea as its western boundary, whilst population and heavy industry tend to be concentrated eastwards in the county. It is a matter of common observation that air pollution in south-west Lancashire is worst when the wind is easterly, and this could more than counteract the greater prevalence of westerly winds.

In males, mortality from cancer of the stomach shows an insignificant correlation with the average population density in the districts surrounding the area, and it becomes zero when the density in the area itself is held constant, indicating no appreciable effect of smoke from adjacent districts on this form of cancer.

Conclusions and Summary

When standardized mortality ratios for bronchitis and cancers in the county boroughs of England and Wales are related to the average amounts of undissolved deposit and smoke from the air in those towns, highly significant statistical correlations are found for bronchitis and lung cancer with both types of pollution after eliminating the effects of population density on the correlations. In all administrative areas in Lancashire and the West Riding of Yorkshire having the necessary pollution data bronchitis is significantly correlated with deposit but not with smoke, whilst for lung cancer the reverse is the case. In Lancashire areas lung cancer is strongly correlated with population density in adjacent districts even when that of the area itself is held constant, and this appears to confirm the effect of wind-borne smoke on the incidence of the disease.

Stomach-cancer mortality is related significantly with both deposit and smoke in the county boroughs, and among females in the Lancashire and Yorkshire districts also, whereas breast cancer shows negative correlations in the county boroughs and no relation with air pollution in the counties. The most likely explanation of this is the exposure of food to dirty air, and this hypothesis is supported by the fact that in the U.S.A., where wrapping of food was the rule long before it began to be practised in Britain, death rates from stomach cancer have fallen steadily in contrast to their lack of improvement in this country. Intestinal cancer also shows small correlations with deposit and smoke in the county boroughs, but they are below the conventional level of significance.

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ASSOCIATION OF GASTRO-DUODENAL LESIONS WITH MÉNIÈRE'S SYNDROME

BY

ROGER WYBURN-MASON, M.A., M.D., M.R.C.P.

That an association exists between the function of the inner ears and that of the stomach and duodenum is shown in various ways. Wolf (1946) recorded the activity of the duodenum both by introducing a balloon into it and by barium-meal investigation, and showed that irrigation of the external ear with cold water caused both nausea and narrowing of the lumen of the first part of the duodenum and replacement of its normal pattern of motor activity by slower and larger contractions. These changes were never seen in the absence of nausea, and vice versa. Clinically, irritative lesions of the labyrinth may result in Ménière's syndrome, which consists of attacks of vertigo, tinnitus, nausea, and vomiting, often accompanied by sweating, faintness, and vasomotor changes, and sometimes by actual syncope. They are often associated with progressive deafness and persistent tinnitus on one or both sides. It must be assumed that a nervous connexion exists by which disturbed function of the stomach and duodenum follows stimulation of afferents in the labyrinth.

Conversely, irritation of the stomach and duodenum by poisonous substances or other agents or by gross distension often leads to nausea, vomiting, sweating, tinnitus, and vertigo, symptoms suggestive of labyrinthine disturbance. That an undoubted labyrinthine disturbance may result from a gastro-duodenal lesion does not seem to have been observed previously. Below is given an account of a number of cases in which such a relationship was present. Furthermore, it has often been denied that diverticula of the second or third part of the duodenum ever produce symptoms (Hahn, 1929), but Ogilvie (1941) and others (see Aird, 1949; Esther and Waugh, 1957) showed that they certainly can do so. In one of the cases described below a diverticulum appeared to give rise to the symptoms of labyrinthine disturbance. An account of five of the cases follows. Six other cases of Ménière's syndrome in association with long-standing duodenal ulcer have been observed.

Case 1

A woman aged 66 was admitted to hospital giving a 20-years history of periods of severe high epigastric pain about half an hour after meals. Four years prior to examination this was replaced by the sensation of food sticking behind the lower sternum coming on immediately after meals and followed by water-brash and heartburn, and sometimes by vomiting. These symptoms lasted for about 15 minutes. They were worse if she lay flat, so she slept almost erect. Stooping caused oral regurgitation. Two years prior to examination, during a period of exacerbation of symptoms, she suddenly vomited for an hour and next day was violently vertiginous, being unable to rise from her bed or move her head, attempts at which caused violent vomiting. These symptoms lasted for three days and then gradually subsided. After a further three days they returned severely, and after 10 days she noticed marked tinnitus and some deafness in the right ear. During the next two years attacks of vertigo and vomiting of varying duration recurred and there was an increase in the right-sided tinnitus and deafness with a constant feeling of unsteadiness on her feet. She was treated by her doctor with phenobarbitone and "avomine" without any appreciable change in her condition. She was admitted to hospital in an acute exacerbation.

Examination.—She was obese, with lax abdominal musculature, otherwise nothing abnormal was found in the abdomen. B.P. 145/85 mm. Cardiovascular and respiratory systems normal. Hb, 92%. Barium meal and swallow: para-oesophageal hernia of stomach of moderate size, apparently incarcerated, but with no observable regurgitation into the oesophagus and only slight obstruction to emptying of the latter. Duodenum normal. A solitary gall-stone present. Aurist's report (Mr. C. P. Malley): "External auditory meatuses normal. Partial right-sided nerve deafness. Audiogram shows well-marked high-tone deafness on right. Left ear normal. Caloric responses greatly diminished on right, normal on left. The changes are typical of Ménière's disease."

She was kept in bed propped up, treated with a convalescent gastric diet, magnesium trisilicate, 1 dr. (4 g.) t.d.s., p.c., and a mixture containing tincture of belladonna, 10 min. (0.6 ml.) t.d.s., a.c. Both the gastric and vertiginous symptoms rapidly improved and the tinnitus considerably lessened. The deafness persisted, however. After six weeks in hospital she stated that she felt better than she had for 10 years. During the next two years she continued the above regime. She had only occasional recurrences of epigastric discomfort, especially after bending, and slight vertigo, but no severe attacks. Repetition of the audiogram and caloric tests at the end of this time showed no change.

Case 2

A man aged 65 attended hospital giving a 35-years history of periods of gnawing epigastric pain, with intervals of freedom. The pain occurred about two hours after meals and sometimes woke him at 1–2 a.m. It was unrelieved by taking a meal. He also suffered from flatulence, and breaking wind relieved the pain. His appetite was poor and he was afraid to eat because of pain, which was often accompanied by nausea, occasional vomiting, and cold sweats. One year prior to his attendance at hospital the pain became much worse, and a month later, during a particularly severe attack of pain, he became violently vertiginous and thought he was going to fall to the right side. He felt alternately hot and cold and faint; he sweated profusely, and had difficulty in focusing. He was unable to stand for nearly a week and was confined to bed for three weeks. He was treated with "vasano" and phenobarbitone and a dehydration regime, but his symptoms persisted in moderate degree. During the next 10 months the onset of epigastric pain was often followed by recurrent attacks of violent vertigo. The severe symptoms usually persisted for three days, then gradually improved, but after that he constantly felt he was falling. If he looked upwards or downwards or moved his head suddenly, he felt giddy, and external objects seemed to be going round. These symptoms were accompanied by much flatulence.

Examination.—He was well-built but edentulous; there was no evidence of anaemia. Cardiovascular system normal. B.P. 110/70 mm. Respiratory system normal. C.N.S. normal. Abdomen very tender on palpation in mid-epigastrium. Aurist's report (Mr. C. P. Malley): "Bilateral nerve deafness, more marked on right side and especially for high tones. Caloric tests show considerable diminution in responses in right ear. The left appears normal. The condition is typical of Ménière's disease." Hb, 109%. Barium meal; rapid evacuation of barium. A large gastric ulcer present in the pyloric antrum.

He was treated as an in-patient with rest in bed, gastric ulcer regime with "bellergal" tablets, 1 t.d.s., a.c., and pulv. "aludrox," 1 dr. (4 g.) t.d.s., p.c. and at night. After six weeks both abdominal and labyrinthine symptoms were completely relieved, apart from some right-sided tinnitus. At the end of this time a barium-meal examination showed that the gastric ulcer had healed. Repetition of the audiogram and caloric tests showed no change. He was observed for two years, during which time he complained only of an occasional slight feeling of epigastric distension and slight giddiness on rising in the morning, but he had had no severe attacks of vertigo.

Case 3

A man aged 55 was admitted to hospital giving a seven-years history of attacks of vertigo and retching occurring about three times a year, but in the last six months much more frequently. During the vertigo objects appeared to move from right to left. He also suffered from anorexia and water-brash after meals, and felt bloated. The latter symptoms were relieved by alkaline powders. He had no abdominal pain. For six years he had complained of slight bilateral deafness and distortion of hearing, especially on the right. The symptoms came on at any time, sometimes woke him at night, and were unrelated to meals. He gained relief by lying on the left side. He constantly felt giddy with the eyes closed.

Examination.—Cardiovascular system normal. B.P. 145/90 mm. Respiratory system normal. Abdomen: some tenderness on palpation in the mid-epigastrium. C.N.S.: no spontaneous nystagmus; positional nystagmus present with vertigo on inversion of the head. Aurist's report (Mr. W. A. Mill): "External auditory meatuses normal. Bilateral nerve deafness, more marked on right, with loss of hearing for high notes. Caloric responses diminished in right ear. History and findings typical of Ménière's disease, but with some positional element." Haemoglobin 114%. Blood urea 21 mg. per 100 ml. Serum protein, 6.1 g. per 100 ml. W.R. and Kahn negative. E.C.G. normal. Histamine test meal, hypochlorhydria. Barium meal: constant stricture about 3 cm. in length in immediate prepyloric region, not dilating after antispasmodics (Fig. 1). Gastroscopy: No lesion observed.

Laparotomy revealed an adult pyloric stenosis. Partial gastrectomy was performed. The removed specimen showed a narrow pylorus with a circumference of about 3 cm., the pyloric musculature being up to 0.7 cm. thick. Section showed a subacute inflammatory cell infiltration of the mucosa and thickening of the submucosa by fibrous tissue. No ulcer was found. During the next two and a half years he had almost complete relief of all symptoms, except for a slight deafness and occasional mild postural vertigo. Two years after operation repetition of the audiogram and caloric tests showed no change.

Case 4

This man, aged 33, developed nine years previously epigastric pain occurring about two hours after meals. A barium-meal examination showed the presence of a duodenal ulcer, for which he received medical treatment; he

remained symptomless for about five years, after which time pain recurred at intervals of several weeks and lasted three to six weeks. Three years before being seen, at the height of one of these attacks of pain, he was seized with severe right-sided tinnitus and violent vertigo, in which he felt he was falling to the right, and the right ear felt blocked. Over the next month the symptoms gradually improved. After this they had repeatedly recurred, usually at the height of an attack of epigastric pain. The tinnitus varied in severity with the vertigo, and the deafness had gradually increased. He had become nervous of going out by himself.

Examination.—General condition good. No evidence of anaemia. Cardiovascular system normal. B.P. 130/80 mm. Respiratory system normal. C.N.S. normal. Slight tenderness on palpation in mid-epigastrium. Aurist's report (Mr. C. P. Malley): "Auditory meatuses normal. Right-sided nerve deafness. Audiogram: well-marked high-tone deafness on right side. Caloric responses markedly depressed on right." Barium meal: large duodenal ulcer with evidence of old scarring. Hb, 96%.

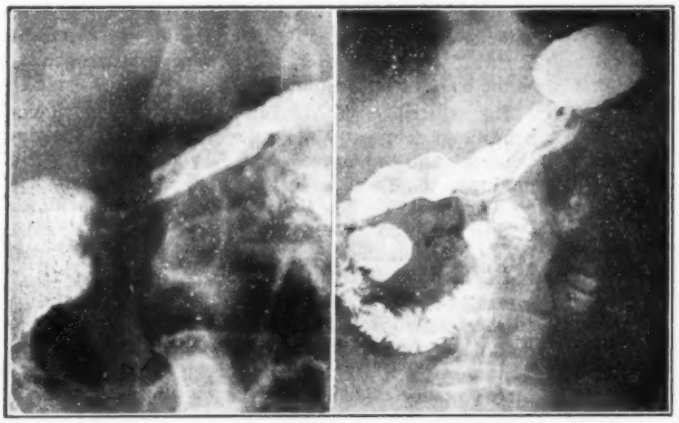

FIG. 1.—Radiograph taken after a barium meal, showing constant stricture in immediate prepyloric region, found at operation to be due to adult pyloric stenosis in association with Ménière's syndrome (Case 3). FIG. 2.—Barium meal showing presence of duodenal diverticula in association with Ménière's syndrome (Case 5).

He was admitted to hospital and treated medically with peptic ulcer regime and a mixture containing 10 mm. (0.6 ml.) of tincture of belladonna t.d.s., a.c., and pulv. aludrox, 1 dr. (4 g.) q.d.s., p.c. After 10 days all the symptoms, apart from the deafness and right-sided tinnitus, had disappeared, and during the next six weeks the tinnitus also diminished considerably. On discharge the vertigo had ceased. During the next three years he adhered to a convalescent peptic ulcer regime and had no return of pain and only occasional mild vertigo on rising.

Case 5

For 10 years a woman aged 63 had been subject to irregular attacks consisting of a sudden onset of vertigo, malaise, right-sided tinnitus, and nausea followed within half an hour by epigastric pain, constant and severe in nature, radiating to the midline of the back below the shoulder-blades. This was followed by retching and vomiting, which had no effect on the pain. The pain would last two to three hours, but the vertigo, nausea, and vomiting might continue for three days or more. She was unable to stand during the attacks. She noted that fried food and milk tended to aggravate the condition, but otherwise the attacks had no relation to food. Since the onset of the attacks she had become progressively deaf on the right side.

Seven years after the onset she developed a thrombophlebitis of the left leg, and some months later, during an attack of pain, she became jaundiced and was admitted to hospital. The liver was found to be enlarged three finger-breadths below the costal margin. Its surface was smooth and tender on palpation. There was acute tenderness on palpation over the gall-bladder. The stools were pale and contained excess of fat, chiefly unsplit, and bile was present in the urine. There was no pyrexia. A cholecystogram showed that the gall-bladder failed to give any concentration of the radio-opaque material. For this cholecystectomy was carried out and a large tense gall-bladder was found and removed. Many faceted "mixed" gall-stones were present, but none were found in the cystic or bile ducts. The jaundice died down only slowly after operation, in spite of which the attacks of epigastric pain continued during the next three years. She also suffered from flatulence and had become dyspnoeic, tired, and lethargic. Ten weeks before her last hospital admission she developed an attack of pain and swelling of the left leg, which had persisted, and three weeks later the right leg was similarly affected.

Examination.—Pale conjunctivae and mucosae. Teeth carious. Tongue clean. No lymphadenopathy. Cardiovascular system normal. B.P. 170/95 mm. Lungs normal. Abdomen: well-healed Kocher's gall-bladder incision; acutely tender on palpation in the right hypochondrium; no mass felt. C.N.S. normal. Gross pitting oedema of both legs reaching to the knees. Acutely tender over calves.

She was observed in an attack of epigastric pain and vertigo. She complained that objects were moving round in clockwise direction and to the right. Examination showed a nystagmus with rapid component to the left and slow to the right. There was marked past-pointing to the right. She tended to lean and fall to the left when standing. Marked tenderness and guarding were present in the mid-epigastrium. The symptoms lasted 72 hours, after which all signs had disappeared. Aurist's report (Mr. W. A. Mill): "Marked right-sided nerve deafness. Caloric responses in left ear normal, in right minimal. The findings suggest Ménière's disease." Blood urea, 36 mg. per 100 ml. Fractional test meal; complete achlorhydria. A barium-meal examination showed a large diverticulum present in the second part of the duodenum arising close to the ampulla of Vater (Fig. 2). Supine films showed a filling defect within the diverticulum, possibly due to food residue. Another diverticulum was present in the third part of the duodenum. Intravenous cholecystogram showed the common bile duct a little dilated but not obstructed, as the opaque medium passed very readily into the small intestine. *X*-ray examination of the chest revealed nothing abnormal.

She was given anticoagulant treatment for 20 days, and during this the oedema of the lower limbs disappeared completely. Avomine tablets had no effect on the symptoms. It was therefore decided to resect the diverticulum. Laparotomy revealed numerous adhesions of the omentum in the right hypochondrium. A diverticulum in the concavity of the second part of the duodenum presented into the wound. A dissection of the lateral side of the duodenum was extended round to the pancreas. The diverticulum was dissected down to its neck and excised. Troublesome bleeding occurred from a large vein in the region of the superior pancreatic duodenal vessels.

The excised duodenal diverticulum consisted of a strip of tissue 5.5 cm. long, 1.8 cm. wide, and 0.5 cm. thick. Microscopically the wall of the diverticulum consisted of mucous membrane, muscularis mucosae penetrated by small Brunner's glands, and, outside this, loose fibro-fatty tissue containing lobules of pancreatic tissue.

Post-operatively the attacks of pain and vertigo ceased, but she vomited small amounts occasionally During this period she felt lethargic and tired, and ran a slight temperature, which was found to be due to cystitis. Between the eleventh and the twenty-second day after operation the

blood haemoglobin level fell from 100 to 59%. A blood transfusion of 3 pints (1.7 litres) restored the level to 91%, and it remained normal thereafter. Six weeks after operation she developed a superficial thrombophlebitis of the long saphenous vein of the left leg. A repeat barium-meal examination at this time showed the diverticula still present in the second and third parts of the duodenum. The outline of the former was still irregular. It seemed that the diverticulum which had been removed lay anteriorly and did not fill with barium at the previous examination. Six months post-operatively she had put on 28 lb. (12.7 kg.) in weight, and, apart from right-sided deafness and some oedema of the legs following the thrombophlebitis, she was completely symptomless. During the next four years she had no further attacks of vertigo or epigastric pain, and right nerve deafness of moderate severity persisted. Caloric tests showed the right labyrinthine hypoactivity still present. The blood count remained normal. The barium-meal findings were unchanged at the end of this time.

Discussion

In the above cases symptoms of a para-oesophageal hernia, gastric and duodenal ulcers, adult pyloric stenosis, and diverticula of the duodenum, usually of long standing, preceded or coincided with those of Ménière's syndrome. The onset or an exacerbation of the symptoms of the latter usually corresponded with an increase in those of the gastro-intestinal disturbance. In the six other cases of duodenal ulcer associated with Ménière's syndrome mentioned the same time relationships were observed. Surgical or medical treatment of the gastro-duodenal lesion appeared to cure or stop the progress of the labyrinthine disturbance.

Another patient observed, a man aged 33, was seized with intense vertigo and vomiting lasting five days some nine years previously, and ever since had been subject to vertigo, especially on rising in the morning or on movement of his head in space. Caloric responses were absent in the right ear. No complaint was made of tinnitus or deafness, and the audiogram was normal. The condition corresponds to the vestibular neuritis of Dix and Hallpike (1952). This patient found that taking a meal almost invariably precipitated an attack of vertigo within 15 minutes. The larger the meal the more severe the vertigo. Such observations seem to suggest that the labyrinthine disturbance in the cases described is secondary to the gastro-duodenal lesion and not the mere coincidence of two common conditions. Search of the literature on gastric and duodenal lesions and Ménière's syndrome has failed to reveal any mention of the association of these conditions.

In all the cases described in full the tests for vestibular and cochlear function were abnormal, and in three of the five this was confined to the right side, while in the other two the right ear was more severely affected than the left. In all six cases of duodenal ulcer associated with Ménière's syndrome mentioned, but not described, the labyrinthine disturbance was confined to the right side. This suggests that the most likely connexion between the disturbance of the stomach and duodenum and of the labyrinth is through a nervous reflex and that the labyrinthine disturbance in these cases is neurogenically produced.

In one case (No. 3) symptoms pointing to the gastro-duodenal lesion were absent or minimal, and the latter was only discovered radiologically. It seems possible that such a silent lesion may be present in other cases of Ménière's syndrome. Moreover, hyoscine or atropine often relieves the symptoms of the syndrome. This could be produced indirectly by action on the gut rather than directly on the labyrinth.

In advanced cases of Ménière's syndrome the commonest pathological findings are oedema of the labyrinth, gross dilatation of the endolymph system, albuminoid coagula in the semicircular canals, and degenerative changes in the organ of Corti and hair cells (Hallpike and Cairns, 1938; Hallpike and Wright, 1939; Dix and Hallpike, 1952). Hallpike believed the attacks to be due to a rapid rise in the fluid pressure within the endolymph system owing to an increase in its volume. There are various theories concerning the aetiology of the changes. These include disturbances in water, sodium, or potassium metabolism and allergy. In favour of the latter are reports of Ménière's syndrome in patients with other allergic manifestations. The cases described above, however, suggest a nervous mechanism as the basis of the lesions.

The association of Ménière's syndrome with angio-neurotic oedema and the role of vasomotor nervous changes and abnormal capillary permeability in producing the lesions in the labyrinth have been stressed by Kobrak (1928), Vogel (1929), Dean (1939), Dohlman (1939), Atkinson (1940), and Meyer (1940). Brunner (1939) ascribed the changes to a "vasomotor internal otitis." Others have attributed them to disturbances of sympathetic vasomotor control of the labyrinth (see Fischer and Wolfson, 1943), but experimental observations do not suggest that the dorsal sympathetic has any effect on the vessels of the labyrinth (Strong, 1957). Moreover, there is no evidence to suggest that changes in sympathetic activity lead to oedema of tissues. Furthermore, while claims for benefit in 60% of cases of Ménière's syndrome were made by Passe (1951), dorsal sympathectomy has given disappointing results in most cases (see Johnson, 1954; Strong, 1957). Thus, while disturbed vasomotor innervation of the labyrinthine vessels may play a part in causing Ménière's attacks, the mechanism by which this is brought about is unknown.

The endolymph is produced in the stria vascularis, and its formation is probably through capillary filtration. Ultimately the hydrops of the labyrinth would seem to be due to increased filtration from blood capillaries in the stria. The permeability of the capillaries is largely dependent on the functional state of the local capillary pericytes or macrophages (Volterra, 1925; Volterra and Schupfer, 1934), and I have shown (Wyburn-Mason, 1958) that this is again controlled by activity in the neighbouring naked nerve endings of unmyelinated fibres of the posterior nerve roots and corresponding fibres in the cranial nerves. The afferent and efferent pathways by which labyrinthine irritation affects gastro-intestinal activity are respectively the vestibular and the vagus nerves. It might be expected that these were also the pathways for the reverse reflex. Unmyelinated nerve fibres with naked nerve endings and conducting *centrifugal* impulses of unknown nature are present in the eighth cranial nerve and pass to the cochlear and labyrinth (Lorente de Nó, 1938; Portmann and Portmann, 1954), and afferents are found in the vagus, so that it is possible that these are the reflex pathways by which gastro-intestinal lesions affect the labyrinthine capillary permeability. It may be that abnormal discharges in the unmyelinated efferent fibres in the eighth nerve increase the normal endolymph formation

and that pressure in this way is responsible for the sudden distension of the endolymph system in cases of Ménière's syndrome.

Summary

Reports are given of a number of cases in which a lesion of the stomach or duodenum was associated with Ménière's syndrome. The latter usually followed the symptoms of the gastro-intestinal lesions, and onset or exacerbation of the labyrinthine disturbance was associated with increase in those of the gastro-intestinal lesion. Medical or surgical treatment of the latter relieved the symptoms of the former, suggesting the labyrinthine disturbance was secondary. The significance of the observations in relation to the aetiology of Ménière's syndrome is discussed.

I thank Mr. R. C. B. Ledlie for permission to publish the details of Case 3, Miss A. H. Baker and Mr. R. W. Raven, who operated on Case 5, and Mr. W. A. Mill and Mr. C. P. Malley, who carried out the aural investigations.

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A review of how colour prejudice has developed over the centuries, and some suggestions on how it may be counteracted, are given in a pamphlet entitled *Colour and Commonsense*, by Kenneth Little (Fabian Society and Commonwealth Bureau, 2s. 6d.). In a foreword Mr. Norman Manley, Chief Minister of Jamaica, draws attention to the fact that in his country "a wide variety of races and their admixtures" live together in mutual respect, "in spite of 300 years of colonialism and the legacy of slavery." Mr. Little, who is reader in anthropology at Edinburgh University, traces the growth of the colour bar through the institution of slavery and its rationalization by the racialist myths of the nineteenth century, into which Darwin's ideas on the origin of species were dragged and misinterpreted. In suggesting ways to prevent individuals from forming an antipathy to coloured people the author stresses the need to present children with natural and objective information. As he says: "Younger children are rarely colour-prejudiced." If they are, they have learnt it from their parents, and here he advises on how the press and B.B.C. could help more.

TWO CASES OF AUTO-IMMUNE HAEMOLYSIS AND APLASIA

BY

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It has been recognized for several years that marrow aplasia is the basis of some of the haemolytic crises in congenital spherocytosis (Owren, 1948; Dameshek and Bloom, 1948; Gasser, 1950) and also in sickle-cell anaemia (Singer, Motulsky, and Wile, 1950; Chernoff and Josephson, 1951). More recently, reports have appeared of aplastic episodes in idiopathic immune haemolytic anaemia (Davis *et al.*, 1952; Linke, 1952; Eisemann and Dameshek, 1954; Seip, 1955; Henneman and Falck, 1957). This report records two further cases in which hypoplasia of the marrow was associated with an auto-immune type of haemolytic anaemia. Radioactive ^{59}Fe and ^{51}Cr studies were carried out, using the techniques described by Wetherley-Mein *et al.* (1956, 1958).

Case 1

A man aged 76 was first seen on November 9, 1955, with symptoms of anaemia which had been increasing for two to three months. Examination at this time showed him to be anaemic but with no other abnormal physical signs. Blood examination revealed: Hb, 5.92 g./100 ml.; R.B.C., 1,300,000/c.mm.; P.C.V., 16%; M.C.V., 123 cubic microns; M.C.H.C., 37%; W.B.C., 2,700/c.mm. (polymorphs 45%, lymphocytes 54%, monocytes 1%). The red blood cells showed macrocytosis and anisocytosis, and there were two normoblasts per 200 white blood cells. Platelets appeared to be plentiful. A diagnosis of pernicious anaemia was made on these results, and on November 10 100 μg. of cyanocobalamin (vitamin B_{12}) was given intramuscularly as a therapeutic trial.

He was seen again on November 25, when his symptoms and pallor were more severe and he was a little jaundiced. Blood examination showed: Hb, 3.85 g./100 ml.; R.B.C., 740,000/c.mm.; P.C.V., 10.5%; M.C.V., 142 cubic microns; M.C.H.C., 36.5%; reticulocytes 2%; W.B.C., 2,000/c.mm. (polymorphs 48%, lymphocytes 50%, monocytes 1%). The film appearances had not changed.

Because of this marked deterioration he was admitted to hospital immediately. Further investigations were performed. Aspiration of sternal marrow on two consecutive days revealed a very poorly cellular specimen on each occasion. Only 6% of the cells were erythroblasts, and one-third of these showed transitional megaloblastic changes. Of the remaining cells, 65% were lymphocytes, 5% neutrophil polymorphs, 13% band neutrophils, 6% neutrophil metamyelocytes, 3% neutrophil myelocytes, 1% monocytes, and 1% plasma cells. A histamine test meal revealed no free acid. Serum bilirubin was 1.1 mg./100 ml. and platelets were 47,000/c.mm.

In view of the hypoplastic marrow picture he was treated with repeated small blood transfusions, and because of the transitional megaloblastic appearance of the remaining erythroblasts he was given folic acid, 15 mg. twice daily. ^{59}Fe studies showed the picture of complete functional aplasia of the marrow with a red-cell utilization of only 2%

(see Fig. 1). He was discharged on December 6 after further transfusion, with a haemoglobin of 11.5 g./100 ml., being then regarded as a case of aplastic anaemia.

Within three weeks of discharge he was readmitted with severe anaemia, and blood examination revealed: Hb, 3.68 g./100 ml.; R.B.C., 1,200,000/c.mm.; P.C.V., 11%; M.C.H.C., 33.5%; M.C.V., 89 cubic microns; reticulocytes, 0.3%; W.B.C., 1,700/c.mm. (polymorphs 44%, lymphocytes 54%, monocytes 2%); platelets, 74,000/c.mm. Direct Race–Coombs test, ++; indirect Race–Coombs test, weakly positive against a panel of O cells. Despite difficulty with cross-matching a transfusion of packed red cells was given, and following this a ^{51}Cr red-cell survival test was carried out, using donor cells. This showed an 18% loss per day (normal 1–4%); and, in view of this evidence of severe shortening of the red-cell life, 10 mg. of prednisone was given three times daily. Following this, transfusion had a more prolonged beneficial effect, and within 16 days the direct Race–Coombs test was negative. As a result of transfusion and steroid therapy his haemoglobin rose to 11.5 g./100 ml., and it was then maintained without transfusion at about 13 g./100 ml. for one year despite slow reduction of the steroid dose. This maintenance of a satisfactory level of haemoglobin was good evidence of the functional capacity of the marrow, which was also demonstrated by a rise in the reticulocyte count, which rose from 0.4% in January, 1956, to 4.6% in April. A second ^{59}Fe study at this time showed a normal pattern (see Fig. 1) with 100% utilization of the tracer dose injected. The sternal marrow, which was examined on June 11, 1956, was now found to be richly cellular, in contrast to the previous aspirates.

Erythropoiesis was prominent, the erythroblasts again showing some transitional megaloblastic features. Mature polymorphs were reduced in number and megakaryocytes were still scanty.

This satisfactory clinical and haematological state was maintained in spite of successive decreases in the dose of prednisone and its final withdrawal at the beginning of November, 1956.

In mid-February, 1957, the direct Race–Coombs test became weakly positive again for the first time for 13 months, and there was a fall in the haemoglobin level associated with a rise of reticulocytes (see Fig. 1). Prednisone therapy was again started, and this resulted in a rise of the haemoglobin level, which was maintained over the next month. In early April the patient contracted an upper respiratory infection, and on April 7 was admitted to hospital with bronchopneumonia.

On admission his haemoglobin was 12.1 g./100 ml.; reticulocytes, 1.1%; W.B.C., 1,250/c.mm. (polymorphs 58%, lymphocytes 42%); platelets, 90,000/c.mm. Direct Race–Coombs test positive. His lung infection was treated with penicillin and streptomycin, though the response was rather slow and he was in hospital for six weeks before he was fit to return home. During this period there was considerable depression of marrow function, as shown by the pancytopenia with a low reticulocyte count. Prednisone was given throughout, though the dose had been cut to 5 mg. twice daily for 10 days at the onset of the infection. Once the infection was overcome the haemoglobin level began to rise, reaching a figure of 19.25 g./100 ml. in August. Following this the prednisone was gradually withdrawn and the haemoglobin fell to about 15 g./100 ml. This level has been maintained without treatment for six months with no haematological evidence of occult haemolysis.

Case 2

A man aged 68 was admitted to hospital in October, 1956, complaining of shortness of breath for the past three days. About six months previously a right above-knee amputation

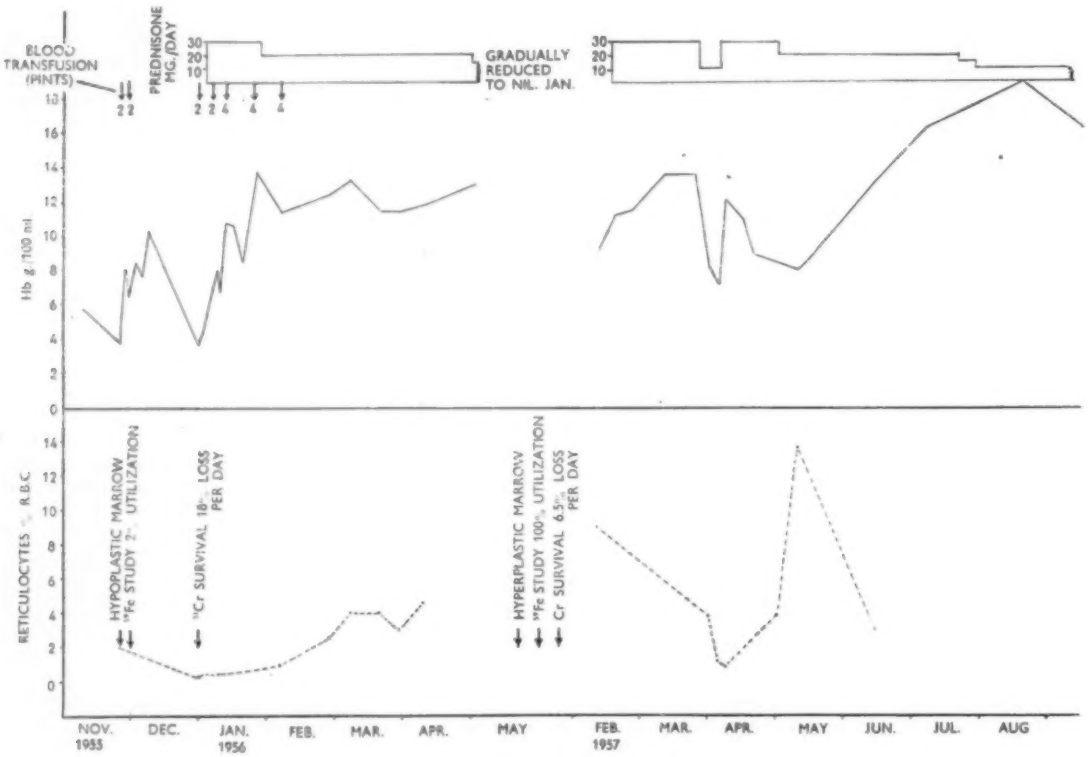

FIG. 1.—Chart of Case 1.

had been undertaken for vascular insufficiency, and in 1931 he had had a gastro-enterostomy for a chronic gastric ulcer.

On examination he was found to be grossly anaemic and had signs of cardiac failure, as shown by a raised jugular venous pressure, crepitations at both lung bases, and sacral oedema. There were no other abnormal physical signs and his spleen was not palpable.

Blood examination revealed: Hb, 3.7 g./100 ml.; R.B.C., 940,000/c.mm.; P.C.V., 11%; M.C.H.C., 33%; M.C.V., 102 cubic microns; W.B.C., 2,400/c.mm. (polymorphs 30%; lymphocytes 54%, eosinophils 16%); platelets, 350,000/c.mm.; reticulocytes, less than 1%. The direct Race–Coombs test was positive. Sternal marrow biopsy revealed a hypoplastic marrow with numerous fat globules in the film. The differential count showed: segmented polymorphs 36%, band polymorphs 13%, metamyelocytes 10%, myelocytes 3%, lymphocytes 10%, eosinophils 9%, eosinophil myelocytes 4%, proerythroblasts 1%, normoblasts A 4%, B 3%, C 7%.

The patient was treated with small repeated blood transfusions, and after about 10 days his haemoglobin had risen to 10 g./100 ml. Throughout this time his direct Race–Coombs test had remained positive, but no atypical antibodies could be detected using the indirect Race–Coombs technique or with trypsinized red cells. A ^{51}Cr survival of his labelled red cells showed a 6% loss of ^{51}Cr per day (normal 1–4%). In view of the evidence of increased red-cell destruction he was started on prednisone, 10 mg. three times a day, and discharged to attend as an outpatient (see Fig. 2). Over the next six weeks his haemoglobin remained around 9 g./100 ml., with the help of two further blood transfusions. ^{59}Fe studies revealed an iron utilization of only 26% (normal 70–80%), confirming that his marrow was still hypoplastic.

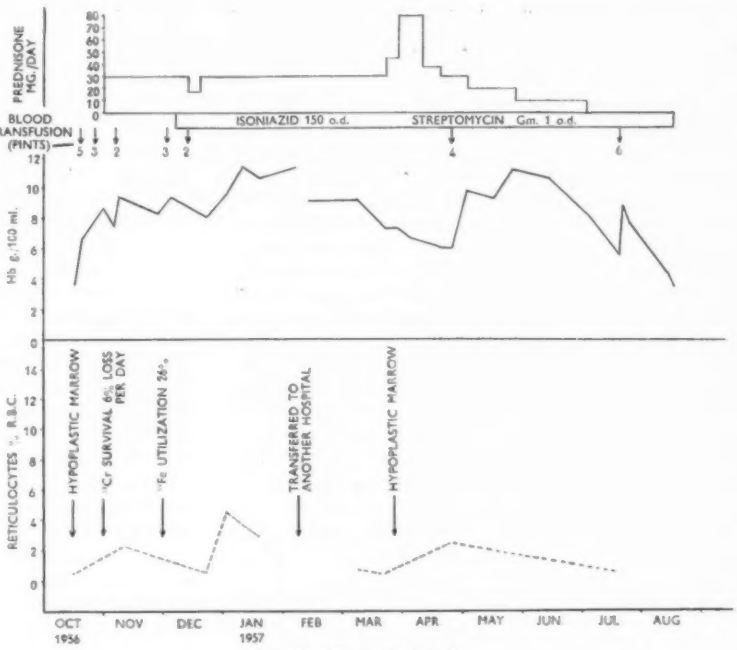

FIG. 2.—Chart of Case 2.

He was readmitted on November 30 complaining of a cough and pain in the right side of his chest. A chest *x*-ray film showed an extensive consolidation of the right upper zone, probably with cavity formation, and tubercle bacilli were found in his sputum. Antituberculous treatment with isoniazid, streptomycin, and P.A.S. was begun, but the P.A.S. had to be withdrawn within a few days because of a high fever. A few days later the prednisone was reduced to 5 mg. three times a day.

A second chest *x*-ray examination about two weeks after the first showed that there had been extensive spread of disease into the left upper and mid-zones and further consolidation of the right lung. His general condition improved slightly over the next two weeks, at the end of which time, when his haemoglobin was found to be only 8.1 g./100 ml., his prednisone was increased again to its previous level. Over the next six weeks his haemoglobin gradually rose to 11.5 g., although he had had no blood transfusion (see Fig. 2). His reticulocytes rose to 4% and his direct Race–Coombs test remained positive, suggesting continuing haemolysis with some recovery of marrow function.

He was then transferred to another hospital to continue his antituberculous treatment. He remained there until his death six months later. On admission (February 15, 1957) blood examination revealed: Hb, 8.5 g./100 ml.; R.B.C., 2,660,000/c.mm.; M.C.V., 103 cubic microns; M.C.H.C., 30%. W.B.C. count 22,600/c.mm. (polymorphs 78%, lymphocytes 19%, eosinophils 2%, monocytes 1%; reticulocytes, 1.8%); direct Race–Coombs test negative. During his stay in this hospital the tuberculous process in his lungs remained active in spite of treatment. His haemoglobin at first remained steady at about 9 g./100 ml., but then dropped gradually to 6 g. despite an increase in prednisone dosage; the direct Race–Coombs test again became positive in March, remaining positive until May 13. His condition was then further complicated by the discovery of positive occult blood in his stools, and on *x*-ray examination he was found to have a small gastric ulcer. Though treatment, with blood transfusions, was given, his condition continued to deteriorate, with sepsis of bedsores and a terminal episode of bronchopneumonia, from which he died on August 20, 1957. His haemoglobin just prior to death was only 3.6 g./100 ml., and this was again associated with a positive direct Race–Coombs test.

Post-mortem examination revealed evidence of basal bronchopneumonia and active fibrocaseous tuberculosis at the right apex. The marrow in the spine and sternum had a homogeneous pinkish-brown colour, but the midshaft marrow in the femur was a little more fatty. There was a functioning gastro-enterostomy but no evidence of an active ulcer at necropsy. The spleen was about twice the normal size and contained a few small infarcts. Histological examination of the tissues confirmed the macroscopical diagnosis of bronchopneumonia and fibrocaseous tuberculosis. The marrow showed hyperplasia of the myeloid elements with a gross reduction in the number of erythroblasts and a normal proportion of megakaryocytes. The spleen showed anaemic infarcts with some hyperplasia of the sinus reticulum, and haemosiderosis. There was no evidence of extramedullary haemopoiesis.

Discussion

The association of a short red-cell life with a failure of red-cell production in refractory and hypoplastic

anaemias was emphasized by Bomford and Rhoads (1941), and in recent years the advent of radioactive techniques has stressed this dual mechanism in many types of anaemia. Loeb *et al.* (1953) reported several cases of "chronic bone-marrow failure" with short red-cell life, but in none was there evidence of an auto-immune mechanism.

Eisemann and Dameshek (1954) report a case with a simultaneous onset of hypoplasia and haemolysis associated with a positive Race–Coombs test; splenectomy was performed on this patient because of failure of response to other therapeutic manœuvres, and the operation resulted in a complete haematological recovery except for the persistence of a weak positive Race–Coombs test. These authors concluded that a splenic factor may have been operating on the erythropoietic tissue in the marrow, causing hypoplasia, or, alternatively, that the specific aregenerative state of the nucleated red cells in the marrow was the result of a direct action of erythrocyte antibodies on the red-cell precursors.

Hennemann and Falck (1957) describe a case of idiopathic acquired immune haemolytic anaemia in a patient who died in a pseudo-aplastic crisis, and a further case of primary aplastic anaemia of three years' duration in a man of 61 who showed latent haemolytic characteristics with a negative Race–Coombs test but who finally developed a fatal haemolytic crisis due to incomplete warm auto-antibodies. They discussed the relationship between haemolytic anaemia and aplastic anaemia and emphasized that their association may lead to difficulties in diagnosis. Crosby and Rappaport (1956) stressed that reticulocytopenia in auto-immune haemolytic anaemia does not necessarily indicate marrow aplasia or an acute aregenerative crisis, but may also be due to alterations in the maturation of erythroblasts or in the life-span of the reticulocyte.

The clinical, haematological, and radioactive studies in our two patients indicate that they had a similar mechanism. They show, in the initial stages of the disease, marked marrow hypoplasia associated with a short red-cell life due to an auto-immune mechanism. In both cases there was gradual recovery of marrow function and also of the haemolytic component associated with steroid therapy. In the first case, reduction of the steroid therapy after stabilization of the haemoglobin led to a recrudescence of the haemolysis, and this was exacerbated by an episode of infection shortly afterwards, which also led to a further phase of marrow depression. The patient made a remarkable recovery from this episode as a result of antibiotic and steroid therapy; the evidence of haemolysis and antibody formation slowly disappeared, and after a frankly polycythaemic phase the patient was haematologically normal six months after stopping steroid therapy. In this case the low white cell count and the platelet count roughly parallel the haemoglobin level, suggesting that a similar process may have been operating for these formed elements.

In the second case assessment of the mechanism is more difficult because of the associated tuberculous infection, and in the later stages because of the evidence of gastro-intestinal bleeding. It is evident that there was some improvement of marrow function associated with steroid therapy as shown by the spontaneous rise in haemoglobin and increase of reticulocytes shown in January, 1957. In the terminal phases of the disease the rapidly falling haemoglobin suggests that both haemolysis and aplasia were contributory mechanisms, though blood loss must also have played some part. Although there is evidence in both cases to indicate the place of infection in their exacerbations there is no evidence that they initiated the process.

The close association between the degree of haemolysis and of marrow function in these cases suggests that the concept of antibody effect in erythrocyte precursors in the marrow may well be correct (Eisemann and Dameshek, 1954), and this is further borne out by the effectiveness of the steroid therapy, which is known to reduce antibody production in auto-immune haemolytic anaemia (Fudenberg *et al.*, 1958). This theory, however, fails to explain why these aplastic phases are not more common in idiopathic immune haemolytic anaemia, unless it is due to some undetected specific feature of the antibody or, alternatively, to an inherent defect in the marrow. Although a case can be made out for distinguishing cases of aplastic anaemia with haemolysis from cases of acquired haemolytic anaemia with aplasia, this separation may obscure the fact that they have common aetiological factors.

Summary

Two cases of acquired haemolytic anaemia with associated aplasia of the bone marrow are described. In each case there was morphological evidence of aplasia, and failure of red-cell production was confirmed using radioactive iron tracer technique. Evidence of haemolysis was demonstrated by standard serological methods and also by radioactive chromium-tagged red-cell-survival studies.

Remission of the marrow failure occurred in each case, though episodes of pulmonary infection led to an exacerbation of the haemolysis and aplasia.

It is postulated that in these two cases an antibody was present which produced destruction of red-cell precursors in the marrow as well as leading to a shortened red-cell life in the general circulation. The beneficial effect of steroid therapy on these two mechanisms of anaemia would support this belief.

We thank Dr. H. J. Anderson for permission to publish Case 2, and Dr. A. C. Dornhorst for access to Case 1 and for his advice in the preparation of this paper.

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POSTURE OF THE TRUNK DURING THE LIFTING OF WEIGHTS*

BY

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This paper is an attempt to answer briefly three questions, and then to suggest an explanation of the answers based on the relevant anatomy. The questions are: (1) How are heavy weights lifted? (2) What part does the trunk play in this? (3) What damage may be produced? The answers to the first two questions stem from personal observation of a large number of people engaged in their everyday tasks.

Ways of Lifting Weights

One can say at once that people seem to lift their burdens in almost as many ways as there are burdens to be lifted. One familiar heavy weight is the suitcase, which may be lifted either by stooping down, grasping the handle, and then straightening the hips and lumbar vertebrae; or by bending the hips and knees and lifting the case with the trunk held erect. That awkward load, a sack of potatoes lying on the ground, is often first lifted by stooping, clasping it to the bosom and lifting it on a bench, and then humping it on to the back. When first becoming house-owners, many people remove stumps of bushes or trees from the garden by loosening the roots, and then hauling the stump out of the ground with the hands between the knees and the back a little stooping, a large upwards pull being obtained by extending the hips and knees.

In modern industry, most heavy weights are handled by machines, but one still sees barrows full of wet concrete being lifted off the ground by the handles, and hods of bricks carried on the shoulders, and so on. In Covent Garden the barrow has largely replaced porter carriage, but towers of baskets are still, on occasion, lifted on to the head from a stand, the bottom basket being grasped by the hands in front of the chest after first bending the legs, and then placed on the head and the legs extended. This list could go on *ad infinitum*, but it serves the purpose of illustrating this first point—that the manner in which a weight is lifted is dependent upon its size, its shape, its position in space, and the habits of the person lifting it.

The Part Played by the Trunk

When considering the trunk, there is at first sight just as large a variety of parts that it can play. However, after watching numbers of people lifting weights of various kinds, one can say that the part played by the trunk appears to depend more upon the magnitude of the weight than upon other factors. When the weight is small the trunk may be flexed or extended, bent sideways or rotated; but as the weight increases the amount of rotation or lateral flexion becomes less, until there comes a time when the trunk is held in a limited range of positions between the two extremes of simple flexion and straight. Moreover, the heavier the weight the more likely it is that it will be lifted with the trunk held in this straighter position.

It must be emphasized that, although the straight trunk is usually held erect, this is not necessarily so. In the straight position the long axis of the trunk is normally placed parallel with, and as close as possible to, the line of pull of the weight, but this line of pull is not always at right angles to the ground. Anyone who has pulled a large weight up a sloping chute by means of a rope is aware that the trunk is held straight but is also held at an angle to the ground.

So one can say that, although with light weights the trunk may be placed in any position, with the greatest loads it is nearly always held erect in a straightened posture. One further observation is relevant, and that is, with large weights the active movement of lifting appears usually to be achieved by movements of the limbs rather than of the trunk.

Lesions Caused by Weight-lifting

A review of the literature makes it apparent that lesions caused by weight-lifting rarely appear in the limbs, but are not uncommon in the trunk. We all know that herniae and prolapses can be precipitated by weight-lifting, and anyone who does a bit of spare-time gardening can testify that repeatedly lifting a weed- and clay-laden spade can cause lesions of the soft tissues of the back even though an exact diagnosis cannot always be achieved in such cases. Our orthopaedic and neurosurgical colleagues spend much of their time dealing with patients who have lesions of their intervertebral disks, disorders in which acute symptoms often first appear when the patient tries to lift some large and heavy article.

There thus appear to be two basic types of injury to the trunk. There is an anterior, *extrusive* group of injuries, which includes visceral herniae and prolapses; and a *spinal* group, including such lesions as lumbo-sacral strain, prolapsed intervertebral disks at the lumbar and cervical levels, tears of posterior ligaments and spinal muscles, and the less frequent crush fractures of the bodies of the lower thoracic and upper lumbar vertebrae.

Anatomical Considerations

In trying to give an anatomical explanation of these various observations it is convenient to divide the analysis into two stages. Firstly, by examining the forces exerted on the trunk when weight-lifting in the different positions; and, secondly, by examining the mechanisms whereby the trunk may sustain these forces. For the sake of brevity this analysis has been limited to the two extreme positions which may be adopted when lifting heavy weights—namely, the straight or erect position and the flexed or stooping position; in each case it has been assumed that the weight is divided equally between the two hands.

Forces Acting on the Trunk

By palpating the muscles of subjects lifting weights in different positions, one can assess the relative strengths of contraction of the various muscles involved. In theory, it would be better to do this with the electromyograph, but in practice the movements of the trunk grossly disturb the record and render it nearly useless. The descriptions given here are based on palpation alone. There appear to be very different patterns of contraction in the two positions.

In the *erect* position the weight is transferred to the humerus by the forearm muscles, and then appears to

*Read to the Section of Anatomy and Physiology at the Annual Meeting of the British Medical Association, Birmingham, 1958.

be carried to the pectoral girdle mainly by the deltoid (Fig. 1). From the lateral part of the pectoral girdle most of the weight is then transferred to the middle and lower cervical vertebrae through trapezius and other muscles. Rotation of the scapula is prevented by the muscles attached to the chest wall. So that, in this erect position, the weight is transferred principally to the neck vertebrae, some reaching the upper thoracic spine.

In the *stooping* position the weight is transferred to the humerus as before, but from the humerus it takes a very different path. The deltoid plays little part (Fig. 2). Anteriorly, a small part of the weight is transferred to the thoracic cage by the pectoral muscles, and thence through the ribs to the thoracic vertebrae. Posteriorly, some of the weight is transferred to the scapula by the rotator cuff muscles and thence reaches the thoracic vertebrae through the lower parts of the trapezius and allied muscles. Below this level the latissimus dorsi can be felt to contract strongly, passing some of the weight to the lower reaches of the spine and the back of the pelvis. In essence, these posterior muscles form a broad sheet which suspends the weight and passes it to the whole length of the thoracic and lumbar spine.

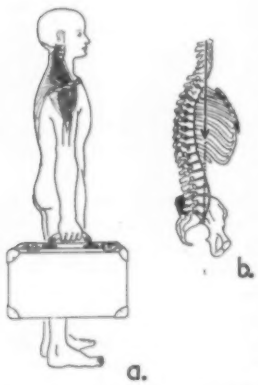

FIG. 1. — In the upright position much of the weight is transferred through the shoulder muscles to the pectoral girdle, and thence to the cervical vertebrae (*a*); it thus exerts a vertical compression upon the trunk (*b*), little muscular contraction being needed for the trunk to sustain the weight. (Drawn by Mrs. M. Besterman.)

When the two paths are compared, it is obvious that in the erect position most of the weight is being transferred to the upper part of the vertebral column. On the other hand, in the stooping position the weight is being transferred to the thoracic and lumbar series and the pelvis itself.

From the mechanical aspect, in the erect position there is a force applied to the cervical vertebrae which acts in the long axis of the trunk, whereas when stooping there is a flexing force acting at right angles to the long axis of the trunk, with its centre at about the level of the fourth or fifth thoracic vertebra.

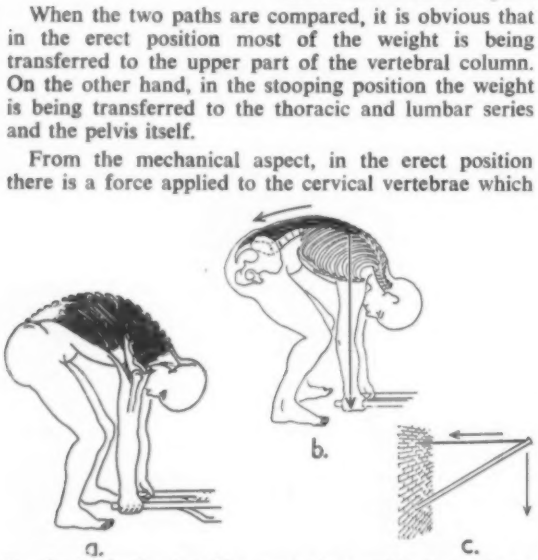

FIG. 2.—In the flexed position much of the weight is transferred direct from the humerus to the lower thoracic and lumbar spine, the remainder passing to the scapula and thence to the upper and middle thoracic vertebrae (*a*); the weight thus exerts a flexing force upon the trunk, and this is resisted by the erector spinae muscles and the vertebral column (*b*), which act together in a manner similar to the ropes and pole of a gaff-staff (*c*). (Drawn by Mrs. M. Besterman.)

Mechanisms Resisting the Different Forces

There is general agreement that vertical forces are resisted by the chain of vertebral bodies and intervertebral disks, a chain well adapted to sustain considerable compression. In the erect position much of the weight acts vertically on the cervical vertebrae, the weight passing directly down the bodies to the thoracic vertebrae. Morphological studies suggest that in some cases the chain of oblique articular facets may well carry some of the vertical force downwards as far as the last cervical or first thoracic vertebra, whence the weight probably passes forwards along the relatively large pedicles to reach the upper thoracic vertebral bodies. This suggestion requires experimental confirmation before it can be accepted. The ribs and sternum brace the thoracic kyphos, and thus sustain some of the weight in the upper thorax, but below mid-thoracic level the chain of vertebral bodies and intervertebral disks is the only apparent means of sustaining vertical forces, for the thoracic and lumbar articular facets lie in a nearly vertical plane and under experimental conditions merely slide up and down if vertical forces are applied.

The lumbar lordosis places the vertebral bodies in the centre of the lower part of the trunk, and Floyd and Silver (1950, 1951) have shown electromyographically that little or no muscular effort is needed to maintain the erect trunk in a position of balance, so that it seems unlikely that much muscular contraction is needed to maintain the erect position of the trunk when carrying weights. The lower lumbar series of disks are wedge-shaped, as are the lowest one or two vertebral bodies, so that vertical forces tend to slide the column forwards on the sacrum and deposit it in the pelvis. This tendency is resisted by the ilio-lumbar ligaments, and by the articular facets of the lumbo-sacral joint, which face principally forwards in most cases.

Since little or no contraction of the lumbar muscles is involved, one can quite easily make an estimate of the downwards force acting on the lower lumbar vertebrae. This force consists principally of the weight of the body above this level, plus the weight being carried by the arms, plus any additional force arising from the acceleration of the weight during the lift.

In the stooping position two mechanisms appear to be involved. The weight, acting as a flexing force on the trunk, is sustained in part by the contraction of the erector spinae group of muscles, which over simply may be thought of as suspending the vertebral column in the same way as wire stays suspend a horizontal flagpole. The fibres of the erector spinae pass obliquely between their attachments, so that the force of their contraction can be split into two components—a dorsal extending force, which is the component used to lift the weight, and a longitudinal component compressing the vertebral bodies. Owing to the complexity of the muscle, it is very difficult to assess the magnitude of these components in the middle reaches of the spine, but a much simpler computation can be achieved for the forces acting at the lower lumbar joints, provided always that it is assumed that the spinal mechanism is the only one which is in action when lifting in the stooping position.

This last is a false assumption, but it is none the less illuminating to compare the theoretical forces acting on the lower lumbar vertebrae in the two extreme positions (Table I). There is thus in theory a fivefold increase in pressure in the stooping position when compared with the pressure in the erect position.

It has been shown experimentally by Hirsch (1951), Virgin (1951), Hirsch and Nachemson (1954), and others that normal lumbar vertebral bodies are crushed by pressures equivalent to about 1,000 lb. (454 kg.) weight, and that such a pressure may well result in permanent deformation of the intervertebral disks. And yet weights greater than 70 lb. (32 kg.) can be lifted by normal male adults in the stooping position.

The answer to this apparent enigma is simple, and is suggested by the extrusive group of lesions and by the suppressed grunt or gasp that accompanies heavy

TABLE I.—*Theoretical Pressure (lb.; kg. Weight) on Body of Fourth Lumbar Vertebra During Weight-lifting. It Has Been Assumed that Only the Spinal Mechanism is in Action. (Based on an Average Normal Male, 5 ft. 10 in. (152 cm.) in Height)*

	Erect		Stooping	
	lb.	kg.	lb.	kg.
Holding 70 lb. (32 kg.) still against gravity	140	63·5	700	317·5
Pressure induced by initial acceleration of weight	80	36·5	350	159
Total pressure during early stage of lift	220	100	1,050	476·5

lifts. Measurements of intra-abdominal pressure in the stooping position show that large increases in pressure occur during the initial heave of a lift, and that a smaller sustained rise of pressure occurs while the weight is held against gravity. With large weights the pressure can rise by up to 100 cm. H_2O. Intra-oesophageal measurements have shown that pressures of a similar order are induced within the thorax. Serial measurements of this rise in pressure show that, for a given weight, there is an almost linear relationship between the pressure induced in the trunk cavities and the angle between the trunk and the ground, there being no significant rise in pressure in the erect position. It would appear that in the stooping position the pressure in the trunk, produced by contraction of the abdominal wall muscles, presses upwards on the ribs and downwards on the pelvic floor to act as an extensor of the trunk and thus to sustain a considerable portion of the flexing force induced by the weight. It can be calculated that about one-sixth of the weight is supported in this way, so that a more real estimate of the pressure on the spine can be obtained, as is shown in Table II.

It must be stressed that these figures are only rough estimates, but they accord well with the observed facts. On the basis of two mechanisms in the flexed position, the theoretical maximum lift is of the order of 140 lb. (63.5 kg.), and few people can lift more than this when stooping. When erect, the theoretical maximum lift is of the order of 500 lb. (227 kg.), and this figure is achieved by professional weight-lifters. It is interesting to note that these sportsmen are trained to keep their trunks as erect as possible when engaging in maximum lifts.

There thus appear to be two mechanisms in the trunk which act together during weight-lifting, the *spinal* mechanism and the pressure or *pneumatic* mechanism; it is suggested that these are involved respectively in the production of the spinal and extrusive groups of lesions. In the spinal group, lesions of the disks would appear to be precipitated by the "nutcracker" effect of

TABLE II.—*Theoretical Pressure (lb.; kg. Weight) on Body of Fourth Lumbar Vertebra During Weight-lifting, Taking the Raised Intra-abdominal and Intrathoracic Pressure Into Account. (Based on Average Normal Male, 5 ft. 10 in. (152 cm.) in Height)*

	Erect		Stooping	
	lb.	kg.	lb.	kg.
Holding 70 lb. (32 kg.) still against gravity	140	63·5	580	263
Pressure induced by initial acceleration of weight	80	36·5	220	100
Total pressure during early stage of lift	220	100	800	363

large compression forces, and are thus more apt to occur in the stooping position. Similarly, the increase in the longitudinal compression force when stooping will increase the liability to ilio-lumbar strain, and the increased tension in the post-vertebral muscles and ligaments may well predetermine soft-tissue injury. In the extrusive group, any potential weakness of the abdominal wall is apt to be broken down by the considerable increase in intra-abdominal pressure, an increase which occurs only when the trunk is flexed.

One must therefore re-emphasize the dictum of former teachers, and say that when weight-lifting it is better to bend the knees than bend the back.

One possible exception to this rule is the person liable to injury of the cervical disks and intervertebral facets. In theory there is less compression force exerted on the neck when stooping than when lifting weights in the erect position: however, the flexion of the cervical spine which accompanies stooping may exacerbate other symptoms present, and it is doubtless best for such unfortunates to refrain from weight-lifting of any kind.

Conclusion

In final summary, one can say that there is evidence that two complementary mechanisms are in action when large flexion forces are resisted by the human trunk, these being the spinal column and its muscles on the one hand, and the "pneumatic" mechanism on the other. Each is affected by its own group of disorders, and in theory it appears that the more flexed the trunk when lifting the more likely is it that damage will occur.

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Although interest in Russian medical work has greatly increased in recent years, the language barrier and unfamiliarity with the existing sources of approach have made difficult the full exploitation of Russian medical literature. This second obstacle has been overcome by the *Guide to Russian Medical Literature* (Public Health Service Bulletin No. 602. Govt. Printing Office, Washington, D.C. 89 pp.; 40 cents). It is edited by Scott Adams and F. B. Rogers and includes chapters describing available Western- and Russian-language sources for Russian medical literature, English translation sources, Russian medical bibliography, medical libraries, medical publishing activities, and a list of current medical journals.

"MAPLE SYRUP URINE DISEASE"

AN INBORN ERROR OF THE METABOLISM OF VALINE, LEUCINE, AND ISOLEUCINE ASSOCIATED WITH GROSS MENTAL DEFICIENCY

BY

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The following case of maple syrup urine disease is the first one to be recorded in this country in this century. Only two definite cases have been reported in the United States.

Case Report

A girl aged 4 months with severe mental deficiency was admitted to the Hospital for Sick Children. She is the first child of healthy non-consanguineous parents, with no family history of mental deficiency. Her condition at birth appeared normal, and breast-feeding was started without difficulty. When 1 week old she stopped sucking and had to be tube-fed. She made slow progress from this time, remaining in hospital for the first three months of life because of feeding difficulty and failure to thrive. At 4 months she was noticed to be jerking her limbs and occasionally to become breathless and cyanosed.

On examination she was a fair-haired, blue-eyed infant weighing 9 lb. 10 oz. (4,365 g.). She was anaemic (haemoglobin 9.47 g. per 100 ml.) and had a mild bilateral seborrhoeic blepharitis. The head configuration was within normal limits and the head circumference 16 in. (40 cm.). There was no control of head movements, although she occasionally attempted to follow a bright light with her eyes. The limbs were thin, with a slight increase of tone, and brisk tendon reflexes equal on both sides. The optic disks were pale. A firm liver edge was palpable one to two fingerbreadths below the costal margin.

Lumbar puncture produced a normal cerebrospinal fluid under normal pressure. The E.E.G. showed an abnormal record with a severe generalized abnormality with multifocal discharges of a kind often seen in those metabolic disorders which are accompanied by seizures. The I.Q. on the Griffiths scale was 55.

The urine was examined to exclude phenylketonuria. The urine was free from protein, and gave a heavy precipitate with 2:4-dinitrophenylhydrazine, but an equivocal reaction with ferric chloride. On smelling a fresh specimen the similarity to maple syrup was detected. On two-dimensional paper chromatography of the urine, valine, leucine, and isoleucine were found in very large amounts. These amino-acids were also present in the blood, C.S.F., and saliva in great excess.

Keto-acids were present in the urine in very large amounts, as were non-keto-acids with the properties of α-hydroxy-acids. The "maple syrup" smell is due mostly to the α-hydroxy-acids, though modified by the keto-acids.

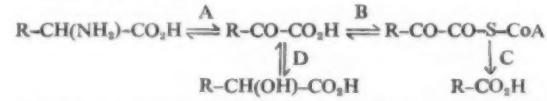
Two-dimensional paper chromatography of the urine for indole derivatives (Jepson, 1955) revealed an excessive excretion of indolylacetic and indolyllactic acid, the other indole derivatives being normal. Abnormal phenolic substances were not detected.

The blood true sugar concentration after a feed was only 60 mg. per 100 ml., non-sugar reducing substances being equivalent to 7 mg. of glucose per 100 ml. Fasting blood apparent sugar concentration (Folin–Wu) was 52 mg. per 100 ml.

Discussion

We suggest that this child is suffering from an inborn error of the metabolism of valine, leucine, and isoleucine, similar in some ways to phenylketonuria.

Coon, Robinson, and Bachhawat (1955) have shown that these three aliphatic amino-acids are metabolized as follows: (A, B, C)



where R = isopropyl, isobutyl, or sec-butyl. We suggest that stage B or stage C is blocked in this child (very possibly through the absence of an enzyme), that there is a build-up of keto-acid and hence amino-acid, and that some keto-acid is reduced by the (abnormal) path D. The three amino-acids with their keto-acids and hydroxy-acids are therefore excreted in large amount.

Unlike what occurs in phenylketonuria, the keto-acid is the normal major metabolite and builds up through the failure of the second link in the metabolic chain. We suggest that, as in phenylketonuria, the abnormal metabolites and/or amino-acid concentrations cause the cerebral dysfunction; they also interfere with tryptophan metabolism, thus causing the observed excretion of indolylacetic and indolyllactic acids exactly as in phenylketonuria.

Menkes, Hurst, and Craig (1954) reported four cases, in one family, of severe progressive cerebral dysfunction, associated with the presence in the urine of an organic acid smelling like maple syrup. Westall, Dancis, and Miller (1957) reported one case of "maple syrup urine disease" with raised blood and urine concentrations of valine, leucine, and isoleucine. Our case seems very similar to this one, and it is probable that the explanation advanced here will cover both cases. The similarity to the four cases of Menkes *et al.* (1954) is perhaps less close, since they found in their cases a decreased excretion of α-amino-nitrogen. Their cases had proteinuria, and the outcome was death within a few days or weeks of birth. Smith and Strang (1958) described the case of a child with a disease which, if not the same as in our case, was very similar.

The hypoglycaemia is not severe enough to account for the mental state. At the moment no explanation can be given for the occurrence of hypoglycaemia in this case, though it is tempting to try to link it to the leucine-precipitated hypoglycaemia described by Cochrane, Payne, Simpkiss, and Woolf (1956).

A diet low in valine, leucine, and isoleucine might help this child, just as a low phenylalanine diet causes improvement in some cases of phenylketonuria (Woolf, Griffiths, Moncrieff, Coates, and Dillistone, 1958). However, there is no economically practicable way of preparing such a diet in the amount needed for a lifetime. In any case, the degree of mental damage is such as to make it unlikely that the child's mental condition would be greatly improved. Nevertheless, a short trial of such a diet is proceeding in order to see whether the abnormal amino-acids and metabolites vanish from the urine. The prognosis in this condition may be worse than in phenylketonuria, the patient of Westall *et al.* dying at 20 months and other children with what is probably the same or a similar condition also dying young (Menkes *et al.*, 1954; Smith and Strang, 1958).

The resemblance to phenylketonuria is so marked that a similar genetic mechanism suggests itself, especially as the four cases of Menkes *et al.* were in one family. This aspect is being pursued.

After this paper was written we heard that Cusworth, Dancis, Menkes, Miller, and Westall had independently found keto-acids in the urine of their cases and identified them as the α-keto-acids corresponding to valine, leucine, and isoleucine (Westall, private communication). A possible explanation of the presence of keto- and hydroxy-acids in the urine in their cases, while the urinary concentrations of the parent amino-acids were not always raised, would be that the blood and tissue keto-acid concentration has to build up to a critical level before enough amino-acid is formed by transamination to exceed the renal threshold. The reverse situation holds in phenylketonuria, where the blood phenylalanine concentration has to build up to a critical level before phenylpyruvic acid appears in the urine. The alternative explanation, that the metabolic error is becoming more severe and more extensive with time, seems unlikely; it would suggest an acquired rather than an inborn error of metabolism.

This condition could easily be mistaken for phenylketonuria. Clinically they are very similar, they give exactly similar reactions with 2:4-dinitrophenylhydrazine reagent and identical urinary indole patterns. However, the ferric chloride reaction, while somewhat similar, is not identical in the two conditions. The smell of the urine is easily missed, and can be masked by preservatives; in this case the smell was not noticed until we deliberately examined the urine for it, having been led by the chemical reactions to consider "maple syrup urine disease" as a possible diagnosis. Acidification with dilute sulphuric acid in the cold enhances the smell considerably; it may be worth investigating, in this way, every case diagnosed as having phenylketonuria. Of course, amino-acid chromatography can differentiate the conditions conclusively.

"Maple syrup urine disease" is not a satisfactory name for the condition. Although one could use for example "leucic aciduria," there is no logical reason for picking one rather than another substance in the urine to provide a name for the disease. If it is confirmed that the metabolic defect suggested above is the cause of the condition, "carboxylase deficiency disease" might best meet the need.

Further work on the identification of the abnormal substances present in the body fluids and on determining the site and extent of the metabolic defect is continuing.

Summary

A grossly mentally retarded infant was found to excrete large amounts of keto-acids; these were identified as the α-keto-acids corresponding to valine, leucine, and isoleucine. The free amino-acids were also found in great excess in the urine, blood, and C.S.F. The urine had a characteristic smell resembling maple syrup; this seems to be largely due to the α-hydroxy-acids corresponding to valine, leucine, and isoleucine. It seems probable that this is an inborn error of the metabolism of the three amino-acids with a block at the oxidative decarboxylation stage. Tryptophan metabolism is also interfered with, as in phenylketonuria. Differentiation of this condition from phenylketonuria needs special care.

We thank Professor Alan Moncrieff for permission to study and report this case and for his interest in the work; the Research Committee of the Hospital for Sick Children for a Research Fellowship awarded to one of us (L. I. W.); Professor Sir George Pickering for kindly providing laboratory facilities; Dr. G. Pampiglione for the E.E.G. report; Dr. W. W. Payne for determining the fasting blood sugar; the nursing staff for their untiring co-operation; and Mrs. S. Phillips, Miss J. Wise, and Mr. P. Cousins for their expert technical assistance.

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"MAPLE SYRUP URINE DISEASE"

BY

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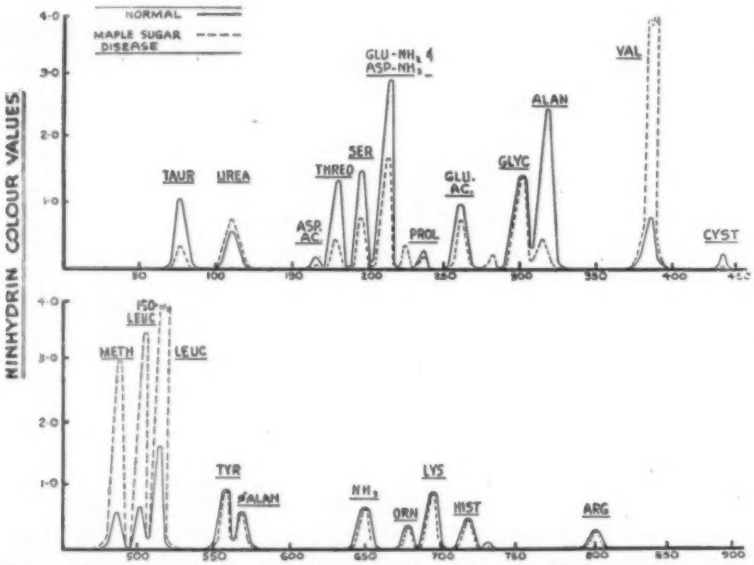
Menkes, Hurst, and Craig (1954) described a familial syndrome characterized by early onset of central nervous system symptoms, a maple syrup odour to the urine, and a fatal outcome. We have more recently studied a similar case, that of a child, in which the characteristic odour of maple syrup was first noted in the urine when he was 4 months old.

The patient was obviously mentally retarded and died at the age of 20 months, the longest survival on record. Samples of urine and plasma collected shortly before death and analysed by the Moore and Stein (1954) method revealed elevations of the branched chain amino-acids—leucine, isoleucine, and valine—strongly indicating a block in the further metabolism of these amino-acids. Other abnormalities were a high methionine and low cystine level, and reduced levels of several other amino-acids, notably alanine, serine, and threonine (see Fig.). Transaminase activity (Awapara and Seale, 1952) for the branched chain amino-acids was demonstrated in the tissues of the patient obtained at necropsy, indicating that the block lay somewhere below the level of the formation of the respective keto-acids. These observations have been previously presented (Westall, Dancis, and Miller, 1957; Westall, Dancis, Miller, and Levitz, 1958). Menkes (personal communication) later succeeded in demonstrating the keto-acids of leucine, isoleucine, and valine in the urine of this patient, adding significantly to the evidence that the metabolic block lay below the level of transamination.

Because all of the observations so far had been made on specimens collected shortly before the death of the patient, it was not clear whether the metabolic block was the primary factor of the patient's disease or a pre-terminal complication. Fortunately a urine from this patient was found that had been collected by the paediatrician a year before death and had been kept in deep freeze ever since. Analysis of this urine failed to reveal an elevation of the branched chain amino-acids, adding temporarily to the confusion. However, it was possible to demonstrate and identify the corresponding keto-acids in the urine (Meister and Abendschein, 1956). It then became evident that the metabolic block was of long standing and probably the primary factor in the patient's disease.



Plasma amino-acid pattern determined by column chromatography (Moore and Stein, 1954). The patient's levels (broken line) are compared with a normal (continuous line).

Quantitative analysis of the urines for keto-acids, using keto-isocaproic acid as standard (Natelson, 1957), demonstrated that the patient excreted 252 mg./24 hours before death and 49 mg./24 hours in the urine collected a year before. This contrasts with figures from three normal infants of 4, 2, and 3 mg./24 hours. The reason for this variation in the amount excreted by the patient is not clear; it may have been due to partial degradation on storage, but it is of interest that it was much higher in the urine where the block "backed up" to involve the amino-acids.

The normal degradative pathway for the branched chain amino-acids is believed to involve oxidative decarboxylation of the keto-acids to the next lower acids —isobutyric, isovaleric, and methylbutyric (Coon and Gurin, 1949). Attempts were made to define more clearly the metabolic block in the patient's tissues. Using leucine-1-^{14}C it was possible to demonstrate that fresh rat tissue (liver, brain, and kidney) was capable of cleaving the carboxyl-carbon from this amino-acid. Unfortunately, tissues obtained from an infant who died of trauma and maintained under identical conditions of refrigeration as those of our patient could not do this. Further study of the patient's tissues, therefore, was not profitable.

The organic acids in the urine are also being investigated with gas phase chromatography. A preliminary analysis has demonstrated eight major peaks, three of which probably represent the keto-acids. It remains to investigate the rest of the peaks as soon as suitable standards are available. The presence of the next lower branched acids—isovaleric, isobutyric, and methylbutyric—must be investigated to locate more exactly the point of metabolic block. If the block lies below the level of oxidative decarboxylation we would expect large excesses of these acids. The possibility that some of these peaks may be attributed to abnormal metabolites, particularly the respective hydroxy-acids of the branched amino-acids, has been entertained and is to be investigated. This was suggested by the recent report that hydroxybutyric acid could impart a "burnt-sugar odour" to the urine of a baby with a disease which may be related to "maple syrup disease" (Smith and Strang, 1958). Also a similar conversion is accomplished by the phenylketonuric in reducing phenylpyruvic acid to phenyllactic acid. We were greatly interested to hear recently that Mackenzie and Woolf (personal communication) have been studying a similar case where they have shown an elevation of the hydroxy-acids as well as the branched chain keto-acids. After exchanging information we decided to arrange simultaneous publication.

At this point it is a matter for speculation whether Menkes's original cases represent examples of the same metabolic disease. From the experience with this patient, it is possible that the normal amino-acid pattern (as distinct from keto-acids) found in the urine of one of their cases does not exclude the diagnosis. However, it will take further experience to decide how pathognomonic a criterion for diagnosis is the maple syrup odour in the urine, since this does seem to have been constantly present.

Summary

The case of a patient with "maple syrup urine disease" is described in which there was an increased excretion in the urine of the branched chain amino-acids leucine, isoleucine, and valine, and also their keto-acid analogues. It is thought that there is a metabolic block of the degradative pathway of these keto-acids in this patient.

It is a pleasure to acknowledge the help of Dr. James Dick, the child's paediatrician, who made the original diagnosis, and Dr. David Cusworth, who identified amino-acids regenerated from the isolated keto-acids. The gas phase chromatography was carried out by Dr. S. Lipsky and Dr. Robert Landowne. The research was aided by grants from the Association for Aid to Crippled Children, and P.H.S. grant 4024, National Institutes of Health.

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TREATMENT OF TRICHURIASIS WITH DITHIAZANINE

A PRELIMINARY REPORT

BY

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Human infestation with whipworm (*Trichuris trichiura*) is said to be world-wide, and both Stoll (1947) and Faust (1949) have estimated that about 355 million persons are affected. Faust stated that the worm is most prevalent in the warm moist regions of the world, where ascariasis may coexist with trichuriasis in the same host, but he gives the incidence of whipworm infestation in Europe as 34 million.

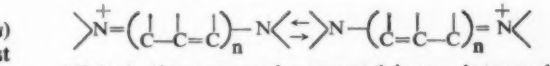
Despite the known prevalence of human infestation, there was no satisfactory treatment until Swartzwelder *et al.* (1957) described the use of dithiazanine against trichuriasis and other worm infestations. Faust refers to the use of oil of chenopodium, carbon tetrachloride, latex of the fig tree ("higueronia"), and emetine hydrochloride, but none of these preparations is considered satisfactory. Jung (1954) described the use of hexylresorcinol enemata; and Dunn (1955) claimed success in 28 out of 31 children treated with piperazine adipate. With the same compound Hoekenga (1956) reported a 50% cure rate from single-dose treatment, but other workers, including Swartzwelder *et al.* (1956), failed to confirm these findings. Hucker and Schofield (1956) observed no therapeutic effect in a trial of four piperazine compounds, used orally, on patients heavily infected with whipworm.

The following report describes the preliminary findings in six mentally defective patients, treated with dithiazanine at Coldharbour Hospital, who were found to be carriers of a moderate whipworm load as judged by faecal egg counts. A more extensive trial is being conducted as larger quantities of dithiazanine become available.

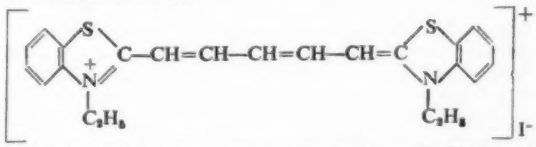
The adult whipworm is usually found in the human caecum, but may also occur in the colon and rectum and posterior part of the ileum. The female worm may measure up to 5 cm.; the male rather less. Trichuris eggs are barrel-shaped, having an outer and inner shell and transparent polar prominences. The eggs measure about 50 μ in the long axis. Infection can occur only by the ingestion of fully embryonated eggs, a process which requires three weeks in a warm moist habitat. After the egg is ingested a further three months must elapse before the worm can complete its development and begin egg-laying. Migration of the larva to other parts of the body does not occur.

The anthelmintic effects of the cyanine dyes, and of dithiazanine in particular, have been investigated by Peters *et al.* (1949) and by Swartzwelder *et al.* (1957). It seems that the action of the cyanines is due to their interference with oxygen uptake and carbohydrate metabolism, and the fact that certain parasitic worms make use of enzyme systems different from those required by mammalian tissues. Bueding and Swartzwelder (1957) have shown that the "amidinium" ion system is responsible for inhibiting oxygen uptake in the filarial worm of the cotton-rat and that cyanine dyes cause an irreversible inhibition of anaerobic carbohydrate metabolism in *Trichuris vulpis*, the whipworm of dogs. In human trichuriasis the cyanines probably affect metabolism in the worm by inhibiting oxidative processes and also anaerobic reactions. Bueding and Swartzwelder state:

> "The amidinium ion system in which a quaternary nitrogen is separated from a tertiary nitrogen by a resonating or 'conjugated' carbon chain of alternating double and single bonds" is illustrated thus:



> "If both nitrogens are incorporated in two heterocyclic rings, such compounds are known as cyanines." The formula for dithiazanine (3,3'-diethylthiadicarbocyanine iodide) is as follows:



Trichuriasis was found by one of us (T. V. C.) at Coldharbour Hospital in January, 1955, when a patient under investigation for loss of weight, anorexia, and episodal diarrhoea showed a large number of eggs in the stools. Other patients subsequently examined also showed unusually high trichuris egg counts, which were in the region of 30,000 eggs per g. of faeces. Further tests revealed that about half the 160 patients in the hospital were infected. Measures to prevent the spread of whipworm have been largely successful, but various therapeutic trials up to December, 1957, gave negative or equivocal results. Following the papers by Swartzwelder *et al.* (1956, 1957), a small quantity of dithiazanine was made available at Coldharbour Hospital, and six patients, known to be carriers of whipworm, were selected for treatment.

Method

In view of the findings of Swartzwelder *et al.* (1957) the trial consisted of a five-day course of treatment with dithiazanine, given orally as 100-mg. "telmid" tablets. These tablets contain dithiazanine covered with a coating of cellulose acetate phthalate and an outer sugar coating.

Two tablets were given three times a day in each case, regardless of age and weight, as reports in the literature had described an almost complete absence of side-effects; and 600 mg. of dithiazanine daily was considered an adequate dose in the adult. Each patient's age and weight, however, are given in Table I. Faecal specimens for egg counts were collected during the three days preceding treatment and for three days immediately afterwards. Further specimens were examined one month after treatment.

For the pre-treatment counts the Stoll technique was used: to previously weighed bottles were added 4 g. of faeces (where multiple specimens were sent, portions from each were taken approximately equal in amount). To each bottle was added 60 ml. of N/10 caustic soda; the bottles were incubated overnight and then shaken in the Kahn shaker to emulsify thoroughly. 0.15 ml. of the emulsion was transferred to 3 by 1-in. (7.5 by 2.5-cm.) slides and covered with 2 by ¾-in. (5 by 2-cm.) coverslips; which gave a relatively thick but visible picture. The *whole* coverslip was counted field by field and the result multiplied by 100 to give the figure per gramme.

Of the post-treatment counts, the pilot examination, immediately after treatment, revealed no ova by the Stoll technique. When specimens were again examined, one month after treatment, all faeces were concentrated and examined by De Rivas's (1928) technique. "Take a few grammes of faeces, emulsify in saline, coarse-filter through muslin, and centrifuge. Re-emulsify the deposit in 5% acetic acid, allow to stand a few minutes, add an equal amount of ether, shake thoroughly, and centrifuge. The top ethereal fluid containing fat, the plug of detritus between this and the acid layer, and the acid layer itself are decanted and the fine concentrated deposit examined microscopically."

Results

The figures in Table I show a complete absence of eggs at the first post-treatment examination. At the second, scanty trichuris ova were present in one case only by De Rivas's concentration technique. From Table II it will be seen that the same patient (Case 3) persistently chewed the telmid tablets and vomited on three of the five treatment days. It seems possible that this patient might also have had a negative result had he not chewed the tablets and vomited.

TABLE I.—*Results of Treating Six Known Carriers of Whipworm With a Five-day Course of Dithiazanine, as Shown by Faecal Egg Counts*

Case No.	Age	Weight in kg.	Pre-treatment Egg Counts. Average per Gramme of Faeces	Post-treatment Egg Counts Immediately after Treatment. Average per Gramme of Faeces	Results of De Rivas's Concentration Technique. One Month after Treatment
1	14	35	2,900	—	—
2	20	47	1,400	—	—
3	14	30	1,300	—	Scanty trichuris ova present
4	19	39	8,100	—	—
5	16	64	3,400	—	—
6	19	35	400	—	—

It will be seen from Table II that a number of adult worms were obtained from each patient. All the worms were non-motile, faintly stained with dye, and apparently dead. They did not appear in the stools of any patient until the third day of treatment, and in two cases (Nos. 1 and 3) not until the fifth day. Since a tendency to constipation was the rule among these patients, it is possible that the use of a laxative or enema, concurrently with dithiazanine, might bring about an earlier clearance of adult worms. Dithiazanine colours the stools blue-green and also seems to have a deodorizing effect.

TABLE II.—*Results of Treating Six Known Carriers of Whipworm With a Five-day Course of Dithiazanine, Showing the Number of Adult Worms Found in the Stools and the Side-effects of Treatment*

Case No.	No. of Adult Trichuris in Stools	Side-effects of Treatment
1	5	Slight rise of pulse rate on second and fourth days
2	72	—
3	10	Tablets chewed. Vomiting on first, second, and fourth treatment days
4	23	Slight rise of temperature and pulse rate, with vomiting on first and second treatment days. Many threadworms on third day. Pallor on fifth day
5	29	—
6	6	Slight rise of temperature and pulse rate on third and fourth days. Vomiting on first treatment day

Side-effects during treatment are shown in Table II. Vomiting in Case 3 has been mentioned. One patient (Case 6) vomited on the first day, when he was apprehensive of swallowing the tablets and chewed a number of them. Another (Case 2) vomited on the first two days of treatment for no obvious reason. Apart from transient elevation of temperature and pulse rate in Cases 2, 4, and 6, and pallor on the fifth day in Case 4, no other toxic effects were noted. The urine was not apparently coloured by the dye. It is of interest that large numbers of threadworms were obtained from Case 4 on the third day of treatment.

Adult whipworms obtained from stools of Case 2.

Swartzwelder *et al.* (1957), after treating more than 400 patients with dithiazanine, noted that associated conditions such as anaemia, malnutrition, cardiac disease, nephrosis, and pregnancy did not influence the tolerance of the drug. The only reactions to therapy which were observed were vomiting and diarrhoea. The same workers carried out extensive laboratory studies of certain adult patients who received 600 mg. of dithiazanine daily for three weeks. They found no subsequent changes in blood urea nitrogen, urine, haemograms, bilirubin, zinc-lipid-thymol turbidities, alkaline phosphatase values, and the prothrombin time. They also found no discoloration or other abnormality in the urine of children treated with dithiazanine.

Conclusions

This preliminary trial appears to provide evidence of the efficacy of dithiazanine against human trichuriasis. In view of the small number of patients treated, the absence of a control group, and the possibility that the six patients chosen might have been influenced by previous trials with other anthelmintics, it is not possible

to provide statistically valid conclusions at this stage. We are conducting a comprehensive trial with dithiazanine, and hope to publish a further report in due course.

Our thanks are due to the nursing staff at Coldharbour Hospital for their care and observation of the patients under treatment. We are indebted to Mr. H. J. Attryde, chief technician, County Laboratory, Dorchester, who personally carried out all the egg counts in the trial. We also thank Eli Lilly and Co. Ltd. for supplying the "telmid" tablets, which were specially obtained from America for this trial.

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STATUS EPILEPTICUS TREATED WITH D-TUBOCURARINE AND CONTROLLED RESPIRATION

BY

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Status epilepticus is a condition in which a series of convulsions occur with such rapidity that in the intervals between them the patient does not regain consciousness. Many authorities agree that the prognosis is poor. Ford (1944) states that where the seizures cannot be controlled signs of exhaustion appear. The temperature rises, respiration is laboured, and tachycardia with signs of circulatory failure becomes evident. The heart may be dilated and pulmonary oedema is often the cause of death.

Small and Woolf (1957) have described severe histological damage to the brain resulting from status epilepticus with respiratory obstruction, and have stressed the dangers of anoxia in this condition, especially in children. It is desirable, therefore, that considerable attention should be directed towards the control and management of the airway in this condition, especially where it does not rapidly respond to the routine forms of treatment. Modern anaesthetic techniques involving the use of muscle relaxants and controlled respiration have proved beneficial in cases of convulsions due to tetanus. That they may also be of value in status epilepticus is shown by the following case history.

Case History

A known epileptic girl aged 11 was admitted to Alder Hey Hospital in status epilepticus. The convulsions were generalized, and began an hour before admission. Intramuscular injections of paraldehyde, 4 ml., phenobarbitone sodium, 1 gr. (65 mg.), and hyoscine, 1/150 gr. (0.43 mg.) failed to control the condition. In spite of oxygen therapy she became cyanosed, and in view of this the aid of the anaesthetic staff was requested.

On examination the child was convulsing and cyanotic, with poor air entry into all areas of the lungs. There was marked masseteric spasm, which prevented the removal of copious blood-stained secretions from the pharynx. The pulse was rapid and weak.

D-Tubocurarine, 15 mg., was injected intravenously, following which the jaw relaxed and the convulsions ceased. After pharyngeal suction, a No. 5 cuffed Magill endotracheal tube was inserted, the cuff inflated, and the tube connected to an anaesthetic machine from which a mixture of 50% nitrous oxide and oxygen was delivered at a flow of 6 litres a minute. Endotracheal toilet was performed and a considerable quantity of secretions removed from the air passages. A carbon-dioxide absorber was introduced into the circuit, and ventilation was maintained by means of a Fazakerly respirator (Esplen, 1956) for 45 minutes. On auscultation there was now good air entry into all areas of the lungs. Scattered crepitations were heard throughout. Soon after the arrest of the convulsions the pulse rate fell from 130 to 110 a minute. Similarly, the temperature fell towards normal after the institution of controlled respiration.

After an interval of 45 minutes, as the effects of the initial dose of relaxant decreased, it could be seen that the convulsions persisted in a modified form. Accordingly, a further 3 mg. of D-tubocurarine was injected intravenously. Controlled respiration was maintained for a further two hours, the patient being ventilated by hand at intervals in order to assess the degree of relaxation.

No further doses of relaxant were required. After three hours the convulsions appeared to have ceased and respiration was assisted manually as it gradually returned to normal.

When the tidal volume was seen to be adequate the supply of nitrous oxide was turned off. The child promptly awoke and coughed on the tube, which was removed after pharyngeal suction. She spoke quietly to the nurse before turning on her side and falling asleep.

The subsequent course was uneventful and she was discharged home.

Discussion

In the severe case of status epilepticus a state of respiratory insufficiency exists which must be relieved. Gaseous exchange is impaired by recurrent convulsions and by respiratory obstruction, while oxygen demand and metabolic rate are greatly increased by muscular hyperactivity. Heat production rises and the resultant pyrexia causes additional oxygen demand. If in addition there is a state of circulatory insufficiency and the heart is dilated, the use of drugs which markedly depress the myocardium would seem to be contra-indicated.

The method of treatment which was adopted in this case provides rapid relief from the state of respiratory insufficiency without the use of agents which add to the cardiac embarrassment. The convulsive irregular respiration of the epileptic state is replaced by controlled respiration. The adequacy of the airway is maintained by an endotracheal tube, and obstructing material in the respiratory passages is easily removed by suction. Trauma to the mouth, teeth, and tongue is avoided.

Both respiratory obstruction and hyperventilation may cause pulmonary oedema. It is known that positive-pressure respiration counters the tendency for an increased amount of fluid to leave the pulmonary capillaries. If, as Ford suggests, death frequently results from pulmonary oedema in this condition, the use of controlled ventilation should be beneficial.

Arrest of the muscular hyperactivity entailed by long-continued convulsions must greatly reduce metabolic rate and oxygen demand. Reference has been made elsewhere (Freier and his colleagues, 1957) to the cessation of sweating, fall in temperature, and slowing of the pulse rate which follow the use of muscle relaxants in convulsive states, and similar effects were noted in the case described above.

Phenobarbitone sodium and paraldehyde are perhaps the most commonly used agents in the treatment of this condition. There is agreement that in many cases they are effective, and that they possess a wide margin of safety. Where these fail to control the convulsions, ether or chloroform by inhalation, or thiopentone by intravenous injection, is often advised.

Diethyl ether may cause a significant degree of myocardial depression (Fisher, Bennett, and Allahwala, 1951). When administered without adequate premedication it results in a copious flow of secretions. Chloroform is noted for its harmful effect on the cardiac muscle and the conducting system of the heart. This latter effect is most likely to occur during induction where the level of circulating endogenous adrenaline is high, as is probably the case in status epilepticus. That thiopentone may cause a reduction in myocardial efficiency has been shown by Prime and Gray (1952). This effect is known to be pronounced in states of circulatory insufficiency. Furthermore, this agent has not the same degree of anticonvulsant activity as has phenobarbitone (Goodman and Gilman, 1955), and its effects may be transient.

Were a patient suffering from hypoxia, obstructed respiration, circulatory failure, pulmonary oedema, and cardiac dilatation being assessed for operation, it is unlikely that the modern anaesthetist would express a preference for such agents or techniques.

In contradistinction, D-tubocurarine has no marked effect on circulatory dynamics in normal dosage (Prime and Gray, 1952), and nitrous oxide is noted for its non-toxic properties. However, D-tubocurarine has no central anticonvulsant action, and should therefore be used in combination with an agent such as phenobarbitone.

Summary

The use of D-tubocurarine and controlled ventilation in a case of status epilepticus with marked respiratory embarrassment is described. Some advantages of this form of treatment are briefly discussed.

I am indebted to Dr. T. Cecil Gray, Dr. G. Jackson Rees, and Dr. Alan L. Stead for criticism and advice in the preparation of this paper, and to Dr. F. P. Hudson for permission to treat the case.

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DIPHTHERIA PROPHYLAXIS

LONG-TERM EFFICIENCY OF SEPARATE AND COMBINED ANTIGENS ADMINISTERED EARLY IN LIFE

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We have previously reported the comparative efficiency of two clinical procedures where infants received their first injection at 3 months of age and were bled at 15 months of age and their diphtheria antitoxin titres measured (Spiller *et al.*, 1955). The two clinical procedures were: (*a*) three monthly inoculations of *Haemophilus pertussis* vaccine, followed by two 0.5-ml. doses of P.T.A.P.—the separate group; and (*b*) three monthly inoculations of combined fluid diphtheria toxoid (30 Lf per dose) with *H. pertussis* vaccine—the combined group. It was found that the geometric mean titre of antitoxin following the separate group was high at 0.883 u./ml. and that the titre following the use of combined prophylactic was also high but not as high as from the P.T.A.P., being 0.54 u./ml. Responses from A.P.T. measured under roughly similar conditions was 0.27 u./ml. (Barr *et al.*, 1950). From this it was concluded that nothing serious was lost in the use of the combined antigen when three doses are given and "alum" is not employed, and that there was much to be gained.

A number of these same children, now 4½–5 years of age, have been bled again and the sera assayed for their diphtheria antitoxin titre. The figures obtained, together with each child's titre at 15 months of age, are shown in the Table.

In the first bleeding—some 7–10 months after the last inoculation in the primary immunization course—there were 81 infants in the combined group and 79 in the separate group. In this present study, some 4–4½ years after the end of the primary immunization course, we obtained 25 sera from the combined group and 28 from the separate group.

As each child was known, it was possible to make individual comparisons and to calculate the geometric mean titres of these two present groups when the members were 15 months of age. Any discrepancy between these latter values and the original total group means would be an index of lack of random sampling. It will be seen from the Table that there would appear to be a discrepancy; in both cases the geometric means of the present two groups when measured at age 15 months are greater than those of the entire groups at 15 months of age: 0.902 u./ml. against 0.883 for the separate group, and 0.80 against 0.54 for the combined

group. The former is obviously not significant. When, however, the appropriate test is applied to the latter (t-test on logs of titres) the resulting value P=0.4 is obtained, indicating no lack of randomness in the children bled the second time in this group.

The geometric mean titre of those children some 4½ years after the end of their course of primary immunization (see Table) is much greater than might have been expected. The two mean titres, of almost equal value, 0.112 and 0.131 u./ml. represent a drop of about one-seventh in the interval of three years (15 months to 4½–5 years) and demonstrate that

Diphtheria Antitoxin Titres of Children, at 4½–5 Years of Age, Who Received Their Primary Course of Immunization at 3–7 Months of Age. "Separate" Group Received Three Monthly Doses of H. pertussis Vaccine Followed by Two 0.5 ml. Doses of P.T.A.P. "Combined" Group Received Three Monthly Doses of Combined Fluid Diphtheria Toxoid With Pertussis Vaccine. (i)=Child's Antitoxin Titre at 15 Months of Age; (ii)=Same Child's Antitoxin Titre at 4½–5 Years of Age in u./ml. of serum

"Separate" Group		"Combined" Group	
(i)	(ii)	(i)	(ii)
2	0·5–1·0	1·25	0·1–0·2
0·8	0·02–0·05	1·25	0·1–0·2
1·25	0·1–0·2	1·25	0·1–0·2
0·8	0·05	1·25	0·5
1·25	0·2–0·5	0·8	0·05–0·1
4	0·05–0·1	3·0	1
1·5	0·2–0·5	0·5	0·02–0·05
0·1	0·02–0·05	0·8	0·02–0·05
0·8	0·2–0·5	0·8	0·2–0·5
2·0	0·1–0·2	0·3	0·2–0·5
2·0	0·05–0·1	0·8	0·1–0·2
0·3	0·1	0·9	0·2–0·5
2·0	0·05–0·1	0·3	0·02–0·05
3·0	0·2–0·5	1·0	0·02–0·05
0·8	0·1–0·2	0·3	0·1
1·25	0·2–0·5	1·25	0·05–0·1
1·25	0·1–0·2	3·5	0·5–1·0
0·3	0·02–0·05	0·3	0·05
0·125	0·01–0·02	0·3	0·1–0·2
1·5	0·5–1·0	0·8	0·1
0·3	0·05–0·1	2·0	0·5–1·0
1·25	0·05–0·1	0·6	0·1–0·2
2·0	0·1–0·2	1·25	0·2–0·5
1·25	0·1–0·2	2·0	0·5
0·8	0·2–0·5	0·1	0·002–0·005
0·2	0·02		
1·25	0·1–0·2		
0·6	0·05		
n=28		25	
Geometric mean, 0·902	0·112	0·800	0·131
s.d., 0·401	0·443	0·358	0·563
Geometric mean of original group of 79 infants, 0·883		Geometric mean of original group of 81 infants, 0·541	

immunization in early infancy with either two doses of P.T.A.P. or three of combined toxoid and vaccine is a remarkably efficient procedure. It is calculated that a geometric mean titre, in a group, of 0.13 u./ml. of antitoxin indicates a 99% Schick-negative reaction rate in that group (Holt, 1955). And over and above this it may be pointed out that every infant was well primed —namely, made a good response to the primary course of immunization (Spiller *et al.*, 1955) and would react rapidly to any trace of toxin due to an incipient diphtheria infection.

Bousfield (1957), who used almost identical reagents as a triple prophylactic for similarly aged infants retested over exactly the same interval of time, found 9 out of 148 such children Schick-positive—a Schick-negative rate of 93.9%.

Nevertheless, because the antitoxin response to diphtheria toxoid (plain)–pertussis mixtures may not be uniformly great, possibly due to variations in the adjuvant properties of different batches of vaccine (Bousfield and Holt, 1957; Holt, 1957), it is to be recommended that children who have been given combined prophylactic in early infancy should receive the usual pre-school booster of fluid toxoid or of fluid toxoid and tetanus toxoid if they had received a primary immunization course of both diphtheria and tetanus toxoid.

Summary

The antitoxin titres of children who had received a course of primary immunization against diphtheria, by either of two clinical procedures, were measured at ages 15 months and 4½–5 years.

At age 15 months the geometric mean titre of diphtheria antitoxin from three doses of *H. pertussis* vaccine followed by two of P.T.A.P. was 0.88 u./ml. of serum, and that from three doses of combined fluid diphtheria toxoid with *H. pertussis* vaccine was 0.54 u./ml. At 4½–5 years of age there is no significant difference between the two means—0.112 u./ml. for the former and 0.13 u./ml. for the latter—which are eminently satisfactory.

Nevertheless, despite these satisfactory results it is recommended that children who have been given combined antigens in early infancy be given a booster dose of toxoid at pre-school entry age. This is because it has been found that the primary responses to combined fluid toxoid and vaccine are not uniformly good.

We gratefully acknowledge the help of other medical officers who assisted with the injections, of Mr. Brian, who gave valuable assistance in the collection of blood specimens, and of the Misses Valerie and Celia Harper for clerical assistance. Thanks are also due to Miss Joanne de Ruiter and Miss Pauline Nellie for help with the antitoxin titrations and to Mr. Tom Norris for care of the animals.

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William Heinemann Medical Books, Ltd., have published a series of five books on sex education, written by Marion O. Lerrigo and Helen Southard in consultation with Dr. M. J. E. Senn. *Parents' Privilege* is intended to advise parents what they should tell children of up to 8 years old about anatomy, conception, and birth. *A Story About You*, for boys and girls in the 9–12-year age group, describes the physical differences between men and women and the changes which occur at puberty, and explains the act of mating. *What's Happening to Me?* provides for teenagers a fuller discussion of physical, mental, and emotional changes which take place during adolescence, with some account of ovulation, fertilization, and birth. *Learning about Love* is a frank discussion of sex problems which may arise among young people from 16 to 20 years of age. *Sex Facts and Attitudes* discusses the physical and emotional aspects of sex, and briefly explains the reproductive system, conception, prenatal development, and birth, for the guidance of those responsible for the sex education of children and adolescents. Each book contains about 64 pages and some coloured drawings and diagrams, and costs about 7s. 6d.

Medical Memorandum

Poliomyelitis Neonatorum with Respiratory Paralysis

It was Falk (1897) who recorded the first case of paralytic poliomyelitis neonatorum, in an infant 15 days old.

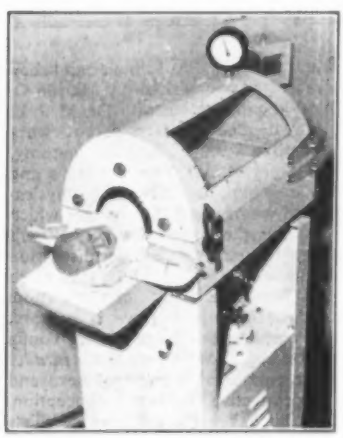
In Britain Gunewardene (1918) reported a widely distributed paralysis occurring in an infant aged 12 days who recovered completely. It was not until 30 years later that neonatal poliomyelitis was again recorded; this time the child becoming drowsy at the age of 4 days, paralysis being established at 11 days (Johns, 1948). In 1950, when a detailed age analysis of cases occurring in England and Wales was introduced, there were four deaths amongst five cases of poliomyelitis notified in the first month of life (80% mortality). During 1951 there were no such neonatal deaths, and in 1952 there were four deaths, three of which occurred in a private home of 13 beds (Sims-Roberts and Thomson, 1953).

In America the literature has been very comprehensive. Talbott Bates (1955) reviewed the literature on poliomyelitis occurring in infants under 1 month of age. He quoted 58 cases, including one he then reported in an infant 40 hours old, which appeared to be the youngest reported in an infant well at birth. Among these 58 cases there were 21 deaths, and eight of the patients who had died had had "anorexia" or "dysphagia," there being no indication of the proportion who had respiratory paralysis.

I have previously reported poliomyelitis neonatorum in an infant aged 10 days (McMath, 1955). Owing to the scarcity of literature upon respiratory paralysis in poliomyelitis neonatorum, the following case is worthy of record.

CASE REPORT

A male infant born on August 19, 1957, was admitted to Neasden Hospital on September 17 with the following history. When aged 17 days he had an infection of the upper respiratory tract and was irritable for the next 10 days. On the 26th day of life his upper limbs and legs became weak, and three days later he was admitted to a hospital, where his breathing deteriorated and he was having attacks of cyanosis. He had received no injections.



The rubber collar (diaphragm) of the baby respirator is placed in the axillae, so enabling the upper limbs to be free for physiotherapy. Photograph by G. A. Booker.

Upon transfer to Neasden Hospital the infant was limp like a "rag doll," with gross paralysis of muscles of the upper limbs, neck, trunk, and, to a less degree, the lower limbs, with no spontaneous movements. Diaphragmatic movement was minimal, whilst there was weakness and inequality of intercostal breathing. His temperature was 98° F. (36.7° C.), pulse rate 158, respiration rate 60. He had a feeble cry and was cyanosed; nor could he feed, insertion of a naso-gastric tube being necessary.

The infant was placed in a cabinet respirator (see Fig.) of the "alligator" type (rate 40 per minute, pressure −10, +0 cm. of water). This corrected the cyanosis. Two days later the respirations synchronized at a rate of 26 per minute with pressures −7, +1 cm. After three days the respirator was able to be opened for five minutes and the following day for 10 minutes hourly.

The infant was gradually weaned from the respirator, and after 14 days his breathing was adequate enough to dispense with it. From this time onwards the severe orthopaedic defects of the upper limbs and trunk were dealt with in the usual manner until his discharge from hospital to the care of an orthopaedic surgeon on November 9.

Diagnostic Procedures.—The patient's cerebrospinal fluid was typical of poliomyelitis, there being 75 white cells per c.mm., and protein 75 mg. per 100 ml. Monkey-cell culture grew poliomyelitis virus type III. HeLa cell culture of the faeces of his brother (aged 23 months) also grew poliomyelitis virus type III, whilst the stools of the parents were negative. This is attributed to the large amount of lymphoid tissue in the child's gut.

COMMENT

Schaeffer and his colleagues (1954) were the first to demonstrate poliomyelitis virus (type I) in the placenta and the aborted foetus of a mother suffering from poliomyelitis: from which they concluded that infection occurred during the viraemic phase in the mother.

Biermann and Piszczek (1944) and Swarts and Kercher (1954) report that neonatal infection can occur orally in the infant at birth from maternal faecal infection or during caesarean section from maternal viraemia, there having been no contact with the mother after delivery or caesarean section.

Most cases of poliomyelitis neonatorum develop after the sixth day of life, from which it would seem that infection, when it occurs, is usually contracted after birth.

In the above case the baby was born healthy on August 19. On August 20 a sibling at home (aged 23 months) developed an infection of the upper respiratory tract with "running nose," cough, and diarrhoea. On the following day the father had an infection of the upper respiratory tract. Both the father and the sibling visited the mother and baby in hospital during the puerperium.

On September 4 the mother developed an infection of the upper respiratory tract, and on the next day the baby (patient) developed an infection of the upper respiratory tract.

Although type III virus was isolated from both the patient's and the sibling's stools, it is impossible to be dogmatic about from whom the baby contracted his infection.

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Reviews

ATMOSPHERIC POLLENS

An Atlas of Airborne Pollen Grains. By H. A. Hyde, M.A. (Cantab.), F.L.S., and K. F. Adams, B.Sc.(Lond.). (Pp. 112 +xvi. 36s.) London: Macmillan and Co., Ltd. 1958.

We have long lacked in Great Britain a book on atmospheric pollens. This atlas has been prepared primarily to form the background of the study of inhalant allergens due to pollen. We would be further indebted to the authors if they would now produce a similar book on airborne fungi. We learn that over 900,000 pollen grains have been counted between 1942 and 1955 at 15 different collecting stations, and that 90% have been assigned to one or other of the 89 different types. The authors state that it is their aim to help beginners in pollen-trapping techniques, as the success of any pollen survey depends upon the recognition of the grains forming the catch. It might, therefore, have been of help if some information had been given as to the time that the various pollens would normally be expected to be caught. Mr. Hyde does not even refer to any of his extensive publications on this subject. This, however, is a very minor criticism of a book that fully reproduces the information which it sets out to give.

The book and all the fundamental botanical work which stems from it in elucidating the general problem of pollen allergy comes from Cardiff, where Mr. Hyde's work has been in some respects a spare-time interest to his general occupation as Keeper to the Department of Botany at the National Museum of Wales. The work from its inception has been stimulated by the Asthma and Allergy Research Unit at St. David's Hospital, Cardiff. Allergists throughout Europe, and particularly in Great Britain, who are in any way interested in the pollen content of the air must have this book for reference. The photographs have been taken from pollen which has been defatted with absolute alcohol or ether and mounted with glycerin jelly using basic fuchsin as a stain. The photomicrographs are of a very high standard and are excellently reproduced in a book at a very reasonable price.

A. W. FRANKLAND.

PSYCHIATRIC PROGRESS

Topics in Psychiatry. The Proceedings of a Specialist Conference in Psychiatry held in Glasgow, October, 1957. Edited by T. Ferguson Rodger, R. M. Mowbray, and J. R. Roy. (Pp. 265+x; illustrated. 20s.) London: Cassell and Co. Ltd. 1958.

Despite a rather uninteresting title, this is really a most valuable psychiatric book. It reports proceedings of a conference in psychiatry, held in Glasgow, at which were discussed a group of psychiatric topics in which progress and synthesis are starting to be achieved at the present time. There is, for instance, an interesting discussion on the psychotherapy and psychopathology of schizophrenia, about which there is greatly renewed interest at the present moment; psychosomatic disorders are discussed from a whole variety of different angles. There are some good articles on the new tranquillizing drugs. There is also an interesting section on mental defect, which gives the ordinary reader a very good idea of some of the active work going on in this hitherto rather stagnant section of psychiatry. A final part of the book contains papers on biochemistry and genetics in relation to mental disorders and mental defect, and includes an interesting article by Professor L. S. Penrose on the "Metabolic Hereditary Disturbances in Psychiatric Illness."

This book can be recommended to psychiatrists and ordinary doctors alike wanting to keep up to date on some of the present rapidly advancing aspects of psychiatry. If more of these conferences were held and reported in this pleasant way it would help us all.

WILLIAM SARGANT.

VIRAL ENCEPHALITIS

Viral Encephalitis. A Symposium. Compiled and edited by William S. Fields and Russell J. Blattner. (Pp. 225; illustrated. 52s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

In cases of acute brain infection the clinician's first responsibility is to investigate very urgently the possibility of some infection of a non-viral type. Thus, many of the bacterial or parasitic infections can be properly cured by modern therapy only if the diagnosis is made early.

This useful little symposium by 10 experts from the Texas Medical Center is concerned with brain infections which are certainly, or at least probably, due to viral infection. A few of these diseases may be accurately identified by clinical features such as the type of paralysis which occurs in poliomyelitis, but in many the diagnosis depends on serological estimation of a rising antibody titre to one particular virus. Difficulty arises in some, such as in von Economo's encephalitis, where the presumed virus aetiology has never been proved. Further, the post-infectious group may well be due to an allergic reaction of the central nervous system, and as such may respond to treatment with cortisone. For most viral encephalitides there is no known specific treatment, and the problems presented by these infections are more hopefully approached by studying methods of prevention. In the last chapter the development of attenuated strains of rabies virus is described, and also current research on attenuated strains of poliomyelitis virus for the development of an oral vaccine. Nearly half of this volume is concerned with an authoritative description of pathological changes of viral disease, with special emphasis on nuclear inclusions.

This collection of papers, which were presented at the fifth annual scientific meeting of the Houston (Texas) Neurological Society, will be useful to many, not only for their description of what is known, but also for indicating the enormous gaps in our knowledge of virus diseases.

W. RITCHIE RUSSELL.

STAMMERING

The Riddle of Stuttering. By C. S. Bluemel, M.D. (Pp. 142. Cloth cover, $3.50; paper cover, $1.50.) Danville, Illinois: The Interstate Publishing Co. 1957.

Why Stammer? By H. St. John Rumsey, M.A.(Cantab.). (Pp. 79. 8s. 6d.) London: Faber and Faber Ltd. 1957.

The precise cause of stuttering or stammering—the term most widely used in Great Britain—remains obscure in spite of the many contributions to the subject. Most recent books have stressed the psychological aspects of stammering and its treatment. Many observers, however, now recognize that several factors in association are concerned in the aetiology of the disorder, not just one factor. It is refreshing, therefore, to find that

Dr. Bluemel believes there is a combination of at least three different causes or situations that lead to stammering: (1) the personality of the sufferer; (2) deficient organization of his original speech; and (3) the incidence of stress which disorganizes the speech function before it is securely established. All these factors, it is stated, must be present to induce stammering. Nevertheless, the author seeks the answer to the problem mainly in the field of psychiatry, and the question of handedness or the struggle for dominance between the cerebral hemispheres is apparently not considered in relation to the second and third possible aetiological factors.

As with most American writers on the subject, Dr. Bluemel attempts to distinguish between stammering and stuttering from the clinical standpoint. Stuttering he regards as "non-organized speech"—speech in the making, with a lack of fluency, or, in other words, immature speech not yet organized into a pattern of oral expression. In Great Britain this condition is usually referred to as "primary stammering." On the other hand, Dr. Bluemel applies the term "stammering" to disorganized speech in contradistinction to non-organized speech—"not speech in the making but speech in the unmaking," a condition termed "secondary stammering" by most authorities. It is advised that treatment be not directed primarily to the speech disorder but to the reorganization of the basic speech, which is better effected in the sensory area than in the motor. Consequently ear training is employed to establish a good pattern of speech. Attention is directed to the thinking process of speech, which is considered more important than the talking process, while the stammerer's phobias and difficulties of personality are regarded as in large measure amenable to psychotherapy. Dr. Bluemel's readable book constitutes yet another noteworthy contribution to the problem of stammering.

Mr. St. John Rumsey's small volume is written mainly for those who stammer, not necessarily to serve as a manual for self-treatment, but rather to explain the nature of their disability and to indicate the means by which the stammer can be treated, especially with the help of a speech therapist. This author is not prepared to accept a purely psychiatric explanation of stammering, and, though his methods of treatment may be dissimilar from those of many other speech therapists, they are to be regarded with considerable respect on account of his long experience in treating speech disorders, especially as speech therapist to Guy's Hospital. Mr. Rumsey's plan of treatment is based mainly on the premise that, as most stammerers sing fluently, a comparatively small adjustment should enable them to speak equally fluently; he advocates, therefore, re-education of the stammerer's faulty speech on vocal lines. The author recognizes that no speech therapist can himself cure a patient's stammer, as such correction must be done by the stammerer himself, preferably under the guidance of the speech therapist. His principles of treatment involve an alteration in the speech pattern by a reduction in the speed of speech, from fast to slow, from a diffident to a firm voice, and from a jerky rhythm to a smooth one. Each step in speech re-education is explained and why such steps are necessary. Mr. Rumsey's book is written very clearly, and is well worthy of study by both speech therapist and patient.

C. WORSTER-DROUGHT.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

Einführung in die Höhere Mathematik für Naturwissenschaftler. By J. Salpeter, 4th ed., edited and enlarged by H. Dallman. (Pp. 412+vi; illustrated. DM. 28.80.) Jena: VEB Gustav Fischer Verlag. 1958.

Holy Tooth. By Edward Samson. (Pp. 125; illustrated. 16s.) Bristol: John Wright and Sons Ltd. 1958.

Short History of Dentistry. By M. Smith, L.D.S. R.C.S. (Pp. 120; illustrated. 13s. 6d.) London: Allan Wingate. 1958.

Polysaccharides in Biology. Transactions of the Third Conference, May 29, 30, and 31, 1957, Princeton, N.J. Edited by G. F. Springer, M.D. (Pp. 249; illustrated. $4.75.) New York: Josiah Macy, Jr. Foundation. 1958.

Practical Blood Grouping. By F. Stratton, M.D., D.Sc., D.P.H., and P. H. Renton, M.D., B.Sc. (Pp. 331+xxiv; illustrated. 42s.) Oxford: Blackwell Scientific Publications. 1958.

Macer Floridus. De Virtutibus Herbarum. Translated and with comments by R. Trifogli. (Pp. 106.) Rome: Istituto di Storia della Medicina dell'Università. 1958.

Akute Innere Krankheiten. Diagnostische und Therapeutische Hinweise in Tabellarischer Übersicht. By H. A. Kühn, H. Klepzig, and E. Schildge. 2nd ed. (Pp. 247+vi; DM. 50.) Stuttgart: Georg Thieme Verlag. 1959.

Courtroom Medicine. Compiled and edited by Marshall Houts. (Pp. 511+xviii; illustrated. £5 5s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

The Amphetamines, Their Actions and Uses. By Chauncey D. Leake, Ph.D. (Pp. 167+xv; 34s.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

Lesions of the Lower Bowel. By Raymond J. Jackman, M.D., M.S. (Pp. 347+xxxvii; illustrated. £5 17s. 6d.) Springfield, Ill.: Charles C. Thomas. 1958.

Temporal Lobe Epilepsy. Edited by Maitland Baldwin and Pearce Bailey. (Pp. 581+xiii; illustrated. £5 17s. 6d.) Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

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YOUR FIGURES IN THEIR HANDS

Since the B.B.C.'s television series "Your Life in their Hands" last year "provoked much public comment . . . by no means all of it favourable," the Corporation's Audience Research team carried out an investigation into viewers' reactions. Its report,[1] now to hand, is as reassuring viewed superficially as it is unconvincing when studied carefully. To discover what is a person's true opinion on a subject he has not been educated to understand, to measure an emotional reaction to it which may range from enjoyment to a horror so strong that he faints and falls into the fire, to choose a person who will be representative of 10,000 other people in these complex reactions, and to summarize it all in a few tables of figures—all this would seem to be a labour of such intricacy that it must have been a surprise even for B.B.C. executives to turn to the end and read the following unsubstantiated conclusion:

> "Did the series cause more (or fewer) viewers to worry, with particular reference to worrying about illness in general?"
>
> "This series does not seem to have made much difference."

Confronted, after the event, with an impossible task, Audience Research did its best to tackle it. The team invited a sample of viewers to attend meetings in London and Manchester, and "to bring along a viewer friend if they wished." It is by no means clear that this technique was ever likely to lead to a sample representative of TV owners, but in response to the invitation 723 attended in London and 141 in Manchester. Unfortunately this attendance represented only about 30% of the invitations in London and 40% in Manchester, so that the sample was in large measure self-selected, and must from the start be regarded with the gravest suspicion for the purpose in hand. It is obviously not sufficient that Audience Research found that "those attending were broadly representative of the viewing public in terms of age, sex, and social class." It is possible, indeed probable, that they were not at all representative in much less obvious but much more important characteristics. Moreover, the difficulties in interpreting their responses seem formidable indeed when we learn that the average viewing public for these programmes was 8 million adults. Inference from such a sample to such a population would seem to demand a degree of recklessness that would land most statisticians in Emergency Ward 10.

Having got their sample of viewers, Audience Research asked them a large number of questions in order to find out to what extent they worried about their health or about illness in general, about going into hospital, about confidence in treatment, and so on. The aim, of course, is to find out whether there was a measurable degree of change in these characteristics after the series had been broadcast compared with before. But no such comparison can in fact be made, for there is no information whatever about the same person "before" and "after." What is done, therefore, is to compare those who saw the series with those who did not, matching these two groups in such a way that it is *believed* that they can be regarded as representative of the desired "before" and "after" situation. These statistically "adjusted" answers of those who chose not to view any of the series are thus labelled "before viewing" and the responses of those who chose to view are labelled "after viewing." It would seem an astonishingly crude method by which to investigate an important problem. An example of how it worked out in relation to "worry" may be cited.

> "The method employed was to list twenty-seven topics about which people might worry and to ask them to underline those which in fact they did worry about. . . . Illness was one of the twenty-seven topics. Before viewing [i.e., the adjusted controls who did not view at all] 24.5% of the London sample underlined illness. After viewing 22% did so. (There were insufficient cases in the Manchester sample to make a precise statement possible, though there too the figures point the same way.) The reduction was greater among 'Heavy Viewers' than among 'Light Viewers.' For the former the figures were: Before viewing 26%, after viewing 22%, and for the latter: Before viewing 22½% and after 22%. It does seem, therefore, that the effect of viewing the series was *not* to increase the incidence of worry about illness but, if anything, to reduce it."

After weighing in these wobbly scales the judgments of this ill-defined sample of TV owners, the research team concludes that the series of broadcasts did not make much difference to worrying about illness or to the amount of anxiety, though "the evidence suggested that viewing programmes in this series tended to increase somewhat the number of illnesses about which people expressed concern." Viewing the series "increased, on the average, the proportion who said they would be 'relieved' (or

[1] *Brit. med. J.*, 1958, **1**, 388.
[2] Ibid., 1958, **1**, 449.
[3] Ibid., 1958, **1**, 510.

'very relieved') to undergo hospital treatment" for various complaints; it "did nothing to diminish the high respect in which G.P.s are held"; "viewers of a particular programme did absorb knowledge from it." "Did the series have a differential effect on 'more anxious' viewers?" asks the report, and it replies: "The short answer is 'No'; the effects of the series on 'more anxious' viewers were very similar to its effects on the average viewer."

Even if the information were sufficient to justify these broad conclusions it would still fall far short of what is needed. We doubt the benefit of this sort of programme of "disease education" to fairly reasonable people much in need of "health education."[1-3] But there can be no doubt of the danger to the unstable with a morbid curiosity about blood and bowels, to the frail worriers, to those with serious disease who may receive interpretations different from those given by their own doctors. Supposing just 1 in 1,000 of those 8 million viewers were seriously and adversely affected—8,000 individuals? Could these small, partially self-selected samples of citizens underlining these answers to elaborate questions be relied upon to reveal that fact? The answer is, No.

MOTHERS OF SCHIZOPHRENICS

In a monograph[1] of unusual interest Y. O. Alanen has given a clear account of the evidence in favour of the rival somatogenic and psychogenic theories of the aetiology of schizophrenia. The somatogenic theory is based on evidence from several fields. Genetical investigations have shown a heavy incidence of schizophrenia in the blood relatives of schizophrenics. Clinical neurology has shown that symptoms of a typically schizophrenic type may be observed in patients with organic diseases of the brain, especially when the temporal lobes are damaged or disturbed. Biochemical, metabolic, and endocrinological investigations have shown differences between schizophrenic and normal people, though none that are both qualitative and consistent. Certain chemical agents, such as mescaline and L.S.D. (lysergic acid diethylamide), produce experimental psychoses in which many of the symptoms are hardly distinguishable from schizophrenic ones. The most effective methods of treatment are the somatic—insulin coma, chlorpromazine, and reserpine.

Those on the other side of Tom Tiddler's Ground, however, have disputed the significance of each and all of these. Referring to the genetical evidence, for instance, M. Bleuler[2] has said that the familial occurrence of schizophrenia is certain, but quite uncertain the interpretation that should be put upon it. Alanen thinks that attempts to show that schizophrenia follows certain and simply demonstrable and describable inheritance of Mendelian type have failed. But some would disagree with this view. Böök's theory of a gene manifesting itself in a proportion of heterozygotes and in all homozygotes has been shown[3] to be capable of accounting for the main results of genetical investigation. The theory may well have to be modified, or even abandoned, with the accumulation of fresh knowledge, but it provides a sufficient working hypothesis for the present. It may, however, be agreed with Bleuler and Alanen that "somatically oriented investigation has not been capable of solving the problem of the aetiology of schizophrenia." That we have not yet reached the goal seems hardly a sufficient reason to abandon our advance and go back to the starting-point.

Alanen then turns to the evidence offered on behalf of the psychodynamic theory. The psychoanalytic psychotherapy of schizophrenia can claim at least three patients, those of Sechehaye, Knight, and Müller, in which recovery from a severe schizophrenia seems to have been attained by this means. Psychoanalytic work has laid emphasis on the significance of maternal deprivation, a disturbed relationship between mother and child, feeding difficulties in infancy, toilet training, and the broken home as factors having a directly pathogenic effect. According to Alanen's review, various investigators have found that about 40% of schizophrenics had come from homes broken before they were 19. Higher proportions, up to 60%, have been found with delinquents. Oltman found for schizophrenia 34.2% broken homes, against 32.2% in controls. Kasanin found an "over-protective" attitude characteristic of the parents of schizophrenics, with rejection infrequent. Tietze, however, found rejection by the mother frequent. Garad discovered no differences between schizophrenics and controls in breast-feeding and toilet training. He found that the mother was not rejective nor punitive; but she was the dominant partner in 66% of cases, and had a markedly heightened relationship with the patient as a child. With regard to fathers, Lidz and Lidz found the predominance of one of three constellations—a father who was in constant battle with his wife, a father who rivalled his son for the mother's attention, and a weak and passive father.

Alanen's own investigation was on the mothers of 100 schizophrenics, and of 20 neurotic and 20 normal controls. The interviews with the mothers were

[1] Alanen, Y. O., *The Mothers of Schizophrenic Patients*, 1958, Munksgaard, Copenhagen.
[2] Bleuler, M., *Lehrbuch der Psychiatrie*, 1955, Springer, Berlin.
[3] Slater, E., *Acta genet. (Basel)*, 1958, **8**, 50.
[4] *Numbers*, chapter 14, verse 18.

generally conducted when the patient was admitted to hospital. The mothers of the schizophrenics, much more than the others, showed signs of anxiety and guilt. Alanen, on grounds unspecified, does not believe that "this difference is due to the fact alone that a child's psychosis is a more upsetting experience for the mother than is a child's neurosis." They were embittered women, with a strong need to talk. They showed anxiety and inward insecurity, proneness to unrealistic behaviour, schizoid traits, aggressiveness, poverty and coldness of emotional life, and lack of empathy. Rorschach tests supported the clinical findings. The women described their own childhood in embittered tones, and disclosed defective relationships with their own mothers. Their marriages were often unsatisfactory, with themselves more often than their husbands as the dominant partner. Their life situations had been of more than usual difficulty about the time of the birth and infancy of the patient. Early mother–child relationships had involved anxiety and aggressions towards the child to an enormously greater extent than in the two control groups. The maternal attitude was not rejective but dominating. They had a firm contact with their children, and that was why their own emotional disturbance affected their children too. They were loveless, and had no understanding for the child's own feelings and needs. This was directly responsible for the weakness of ego development in the child, which eventually led to breakdown.

Unlike work in the somatic field, even the most conscientious and fair-minded investigations of attitudes and character traits suffer from the weakness of depending on observations of a highly subjective nature. The danger may arise, even with the most scrupulous, of interpreting the nebulous findings in accordance with theory. Furthermore, when the limits of normality are themselves not drawn, any attitude or trait can be stigmatized as deficient, neurotic, or abnormal. The observational data on which Alanen depends must therefore be regarded with reserve. The next chain in the argument is also weak. It seems quite likely that the mothers of schizophrenics do differ, as a group, in their temperamental qualities from the generality of the population. It is much more doubtful how far this has a directly pathogenic effect. Finally, one may even accept Alanen's interpretations as cogent and still find it difficult to derive any useful practical consequences. Broken homes, defects in toilet training and feeding habits, and the like were practical matters that the knowledgeable and conscientious mother might hope to correct. As aetiological factors it seems that they have now all been exploded. We are presented in Alanen's case histories with a picture of mothers who were, within the limits of their natures, trying their best, but that best was not good enough. It seems that the family doctor and the welfare worker are to be handed the task of teaching the anxious mother not to be anxious, not to be bossy, nor loveless, nor overprotective, nor rejective. One wonders whether there are any limits to the delinquencies of the modern mother, or whether, perhaps, some of these harsh accusations have not yet been fully justified. Theorists who attribute the primary causation of schizophrenia to a mutant gene are emphasizing the role of a malign chance. For some, the idea of man as the sport of fate is one that is difficult to bear. For the unfortunate mother of a psychotic child it will be less dreadful than the reproach that her child's illness has been her doing. In the eyes of the psychodynamist, however, that is the case; and the guilt rests not only on her but on her mother too. The teaching of Moses[4] is enunciated anew.

MENTAL HEALTH BILL

The Mental Health Bill, which was published earlier this week, appears just over eighteen months after the Report of the Royal Commission on the Law Relating to Mental Illness and Mental Deficiency.[1] In its main provisions the Bill embodies nearly all the important changes recommended by the Royal Commission and by the B.M.A.'s Psychological Medicine Group Committee, which prepared the evidence[2] for Council to submit to the Commission. No doubt as a result of the very detailed examination the Bill will receive in Parliament many minor changes will be made in it, but as it stands to-day it represents a massive administrative advance in the care of the mentally disordered.

The first part of the Bill contains its main clauses. The Lunacy and Mental Treatment Acts, 1890 to 1930, and the Mental Deficiency Acts, 1913 to 1938, are to be repealed; the Board of Control is to be wound up; mental health review tribunals are to be set up in the areas of regional hospital boards to consider applications from patients (and relatives) for their release from hospital; the single term "mental disorder" is to cover all forms of mental illness or disability; and arrangements can be made for any kind of hospital to receive any type of mental patient, whether on an informal basis or under detention.

By removing all the formalities which under the present law must be observed before even a voluntary patient can enter a mental hospital, the Bill will make informal treatment of the mentally ill normal practice; and the same end will be served by removing the present statutory limitations of the treatment of "persons of unsound mind" in "designated" hospitals. But, in their own interests or for the protection of others, some mentally disordered patients, as in the past, will have

to be compulsorily admitted to hospital and detained therein. Part IV of the Bill is concerned with these patients.

Four groups of mentally disordered patients are recognized as coming within the provisions concerned with compulsory detention—mentally ill, severely subnormal, subnormal, and psychopathic. The terms "mental defective," "idiot," "imbecile," and "moral defective" will no longer be used.

"'Severe subnormality' means a state of arrested or incomplete development of mind which includes subnormality of intelligence and is of such a nature or degree that the patient is incapable of living an independent life.... 'Subnormality' means a state of arrested or incomplete development of mind (not amounting to severe subnormality) which includes subnormality of intelligence and is of a nature or degree which requires or is susceptible to medical treatment or other special care or training of the patient.... 'Psychopathic disorder' means a persistent disorder of personality (whether or not accompanied by subnormality of intelligence) which results in abnormally aggressive or seriously irresponsible conduct on the part of the patient, and requires or is susceptible to medical treatment." (This definition of psychopathic disorder is much less wide than the definition suggested by the Royal Commission.)

Patients may be compulsorily admitted to hospital for a period of observation—not more than 28 days—or for a longer period of treatment. In both cases the application has to be supported by two medical recommendations, and one of them must be by "a practitioner approved . . . by a local health authority as having special experience in the diagnosis or treatment of mental disorders." In urgent cases only one medical recommendation need be provided in the first place, but the patient will not be detained for more than 72 hours unless a second medical recommendation is added.

The application for the patient's admission may be made either by his nearest relative or by a mental welfare officer of the local health authority, but generally the mental welfare officer is required to consult the nearest relative and may not proceed (except in emergency) if he objects. Similar arrangements apply to patients admitted to guardianship ("the person named as guardian . . . may be either a local health authority or any other person").

At any time within six months of being compulsorily admitted to hospital a patient may "apply" to a mental health review tribunal; and if the authority to detain him is renewed he has the right again to apply to the tribunal. Unless renewed, the authority lapses at the end of fixed periods—one year, then another year, then two years, and subsequently every three years. The nearest relative of the patient will hold the power of discharge: if this relative unreasonably objects to a patient's admission or would be likely to exercise the power of discharge in a manner contrary to the patient's welfare or the public interest, then any other relative of the patient or a mental welfare officer may apply to a county court for the function of the nearest relative to be transferred to some other person or to the local health authority.

[1] Cmnd. 169, 1957. H.M.S.O., London.
[2] See *Brit. med. J., Suppl.*, 1955, **1**, 211.
[3] Ibid., 1958, **1**, 212.

Other important parts of the Bill are concerned with the admission to hospital of patients convicted of criminal offences, with procedure when children are found to be unsuitable for education at school because of mental disability, and with the management of the property and affairs of patients. An assize court may order that a mentally disordered person convicted before it shall not be discharged from a hospital without the Home Secretary's consent. The power of local authorities are extended somewhat, and provision is made for the continuation of services now provided under the Mental Deficiency Acts. Local authorities will have the duty of registering and inspecting hospitals and nursing-homes for mental patients outside the National Health Service.

This brief review of a long and comprehensive Bill can do no more than point to some of its main provisions. By waiving the formalities relating to the certification of mental defectives, the Government has already shown its adherence to the principle that so far as possible patients should be admitted to mental and mental deficiency hospitals without formality.[3] The Mental Health Bill takes the matter further and much good will come from it. But whether or not the changes brought about by the Bill will be notably and quickly advantageous to patients will depend very much on the attitude of the public to mental illness. The social adaptation of patients discharged from mental hospitals is sometimes precarious. They and their families can receive much-needed support from the aftercare services provided by the hospital and local authority, but without public tolerance the way may still be hard for those who are trying to overcome a serious disability.

MAPLE SYRUP URINE DISEASE

The inborn errors of metabolism, first described by Archibald Garrod fifty years ago, are now being intensively studied by modern chemical methods. Many new diseases of this type have been discovered in recent years. Several of these are associated with mental deficiency—for example, galactosaemia,[1] Wilson's disease,[2] H disease,[3] sucrosuria,[4] and familial goitrous cretinism.[5] The site of the metabolic error has varied widely, but perhaps the disease most studied in its relation to mental defect has been phenylketonuria.[6] Here there is a deficiency of an enzyme required in amino-acid metabolism, with an inability to oxidize phenylalanine to tyrosine: the result is an excessive concentration in the plasma of

[1] Holzel, A., Komrower, G. M., and Schwarz, V., *Amer. J. Med.*, 1957, **22**, 703.
[2] Bearn, A. G., ibid., 1957, **22**, 747.
[3] Baron, D. N., Dent, C. E., Harris, H., Hart, E. W., and Jepson, J. B., *Lancet*, 1956, **2**, 421.
[4] Moncrieff, A., and Wilkinson, R. H., *Acta paediat. (Uppsala)*, 1954, **43**, Suppt. 100, 495.
[5] Hutchison, J. H., and McGirr, E. M., *Lancet*, 1956, **1**, 1035.
[6] Knox, W. E., and Hsia, D. Y-Y., *Amer. J. Med.*, 1957, **22**, 687.
[7] Allan, J. D., Cusworth, D. C., Dent, C. E., and Wilson, V. K., *Lancet*, 1958, **1**, 182.
[8] Westall, R. G., Dancis, J., and Miller, S., *Amer. J. Dis. Child.*, 1957, **94**, 571.
[9] Menkes, J. H., Hurst, P. L., and Craig, J. M., *Pediatrics*, 1954, **14**, 462.
[10] Smith, A. J., and Strang, L. B., *Arch. Dis. Childh.*, 1958, **33**, 109.
[11] Woolf, L. I., *et al.*, ibid., 1958, **33**, 31.

phenylalanine and an outpouring of phenylalanine derivatives in the urine. One of these, phenylpyruvic acid, forms the basis of the simple ferric chloride test for this disease. Last year J. D. Allan and his colleagues[7] described another familial type of mental deficiency related to a distinctive abnormality of amino-acid metabolism. In this disease the urine contains an abnormal peptide in large amounts: this is associated with a low concentration in the plasma but a high level in the cerebrospinal fluid. It is possible that it is formed in the brain, whence it leaks into the plasma and is rapidly excreted by the kidneys.

Elsewhere in this issue of the *Journal* Drs. D. Y. Mackenzie and L. I. Woolf (p. 90), of the Hospital for Sick Children, Great Ormond Street, and Dr. J. Dancis and his colleagues in New York (p. 91) describe yet another disturbance of amino-acid metabolism which results in mental deficiency. This has been called "maple syrup urine disease" because the urine of the patients has an odour of maple syrup or burnt sugar. Acidification with sulphuric acid in the cold enhances the smell. This disease may easily be mistaken for phenylketonuria because the smell of the urine might not be noticed, and the ferric chloride reaction is somewhat similar. The two diseases can, however, be clearly differentiated by amino-acid chromatography.

In maple syrup urine disease the plasma, cerebrospinal fluid, and saliva have abnormally high concentrations of the three aliphatic amino-acids, valine, leucine, and isoleucine. Hypoglycaemia has also been found. Chromatograms of the urine show not only valine, leucine, and isoleucine, but also very large amounts of their corresponding keto-acids and hydroxy-acids. The smell of maple syrup is due to the hydroxy-acids. Transaminase activity for these amino-acids has been demonstrated in the tissues of a patient after death.[8] The finding by Mackenzie and Woolf of the keto-acids in the urine is further proof that the metabolic block lies below the level of transamination. The normal degradative pathway for leucine, isoleucine, and valine is believed to involve oxidative decarboxylation of the keto-acids to isobutyric, isovaleric, and methylbutyric acid. However, the presence in the urine in large amounts of abnormal metabolites—namely, the corresponding hydroxy-acids—suggests that some of the keto-acid is reduced by an abnormal pathway. Mackenzie and Woolf think that decarboxylation of the keto-acids may be blocked by the absence of an enzyme and that "carboxylase deficiency disease" might be a suitable name for the disorder. They also report that chromatography of the urine for indole derivatives showed an excessive excretion of indolylacetic and indolyllactic acid. This evidence of interference with tryptophan metabolism is another point of similarity with phenylketonuria.

The prognosis of maple syrup urine disease is probably worse than in phenylketonuria, since most of the patients reported have died young.[8–10] The presumption that the enzyme defect is genetic in origin is supported by the report of four cases in one family.[9] A diet low in valine, leucine, and isoleucine might be expected to benefit these patients in the same way as a diet poor in phenylalanine improves children with phenylketonuria.[11] At present, however, there is no economically practicable way of preparing such a diet over long periods.

While these inborn metabolic errors each seem to be rare, they are of great importance. The problem of "primary" amentia has long seemed insoluble. Recent work is at last outlining something of the disordered chemistry which may be responsible. With increasing knowledge comes the hope of some rational forms of treatment.

THE INTERMEDIATE MEGALOBLAST

Megaloblastic erythropoiesis occurs in many anaemic states other than classical Addisonian pernicious anaemia. Most of these conditions are associated with defective gastro-intestinal absorption of vitamin B_{12} or folic acid, and they include sprue, idiopathic steatorrhoea, nutritional macrocytic anaemia, megaloblastic anaemias of pregnancy and infancy, and mechanical, inflammatory, or neoplastic lesions of the stomach or intestines. Deficiency of vitamin C, infestation with *Diphyllobothrium latum*, and toxic reactions to certain anticonvulsants may also lead to megaloblastic anaemia. All these disorders are now well recognized to be possible causes of megaloblastic change in the bone marrow associated with a macrocytic anaemia, but their differentiation from classical pernicious anaemia may not be easy, since the clinical picture is often confusing and histamine-fast achlorhydria is by no means confined to pernicious anaemia alone. Measurement of vitamin B_{12} levels in the serum and studies of the absorption of radioactive vitamin B_{12} are helpful in difficult cases, but facilities for such investigations are not always available, and both biological assay of the vitamin level in the serum and adequate isotope studies are time-consuming and costly.

It is therefore appropriate that H. Fudenberg and S. Estren[1] should again draw attention to the intermediate megaloblast and its value in the differential diagnosis of pernicious and related anaemias. Intermediate megaloblasts have long been recognized and described by British authors.[2–4] They are erythroblasts morphologically intermediate between normoblasts and the unequivocal megaloblasts of classical pernicious anaemia. The cytological features characteristic of these cells include a nuclear chromatin pattern more primitive and more finely reticulated than that of normoblasts at a comparable stage of maturity, but coarser in pattern than the corresponding fully developed megaloblasts. The tendency for cytoplasmic maturation with increase in haemoglobin to occur in advance of nuclear maturation, so often a striking feature in cases of pernicious anaemia, is rarely seen in intermediate megaloblasts, but they do show abnormal mitoses and nuclear degenerative changes like those often seen in true megaloblasts. Fudenberg and Estren confirm the

[1] Fudenberg, H., and Estren, S., *Amer. J. Med.*, 1958, **25**, 198.
[2] Trowell, H. C., *Trans. roy. Soc. trop. Med. Hyg.*, 1942, **36**, 151.
[3] Davidson, L. S. P., Girdwood, R. H., and Innes, E. M., *Lancet*, 1947, **1**, 511
[4] Dacie, J. V., and White, J. C., ibid., 1947, **1**, 614.

existence of these cytological differences, and in a well-documented review emphasize the frequency with which intermediate megaloblasts are found in non-Addisonian megaloblastic anaemias. They present evidence in support of the view that these intermediate cells differ from classical megaloblasts as a result of iron deficiency at the site of erythropoiesis, which deficiency is superimposed upon an existing deficiency of vitamin B_{12} or folic acid, and they note that marrow cells in true pernicious anaemia in the early stages of treatment, when iron levels in the serum tend to fall sharply, often somewhat resemble intermediate megaloblasts. Moreover, similar cells may be observed in cases of classical pernicious anaemia complicated by infection, loss of blood, or gastric carcinoma, and the authors believe this to be a consequence of the added factor of iron deficiency. In untreated, uncomplicated cases of pernicious anaemia intermediate megaloblasts are not found. The recognition of intermediate megaloblasts will not present great difficulty to an experienced haematologist, and their presence would strongly suggest that the anaemia under investigation is not true uncomplicated pernicious anaemia.

MORE SMOKE

Tobacco smoking, like road accidents and chemical pollution of the environment, is one of the great public-health problems of our time. These three have a common feature in that a large measure of human volition enters into them. In other words, the risks are widely known; that they continue to exist and even to extend is principally a matter of choice. By contrast, ignorance was often the first obstacle that the great sanitary reformers of the nineteenth century had to overcome.

The latest report from the Customs and Excise[1] shows that smoking increased again in 1957–8 (the twelve months ending March 31). The amount retained for consumption in the United Kingdom was 241,875,436 lb. (110 million kg.). This was 3 million lb. (1.4 million kg.) more than in 1956–7, and 2.6 million lb. (1.2 million kg.) more than in 1955–6. Between 1948 and 1951 the annual increases in consumption were small—about 1 million lb. a year, or 0.5% of the total. But thereafter consumption sharply accelerated, so that from 1952 to 1955 the annual increase averaged about 6 million lb. It then levelled out somewhat and even fell slightly from the year 1955–6 (239.3 million lb.) to the year 1956–7 (339.0 million lb.). The 241.9 million lb. retained for consumption in 1957–8 was a record. To smoke all this tobacco the smokers had the privilege of paying £712m. in tax, a record high figure which was £11m. more than in the previous year. Tobacco has for many years been the largest single source of tax paid to the Customs and Excise. In 1957–8 it composed about one-third of the Customs and Excise revenue and about one-seventh of the Government's total revenue.

The scheme by which old-age pensioners obtained tax relief on tobacco was brought to an end last year by the National Insurance (No. 2) Act, 1957. It began in 1947 and in all cost the nation, in tax remitted, £133m. The numbers of pensioners enjoying relief, states the report, rose year by year from about 1½ to 2¾ million a year.

[1] *49th Report of the Commissioners of Her Majesty's Customs and Excise for the year ended March 31, 1958*, Cmnd. 613. H.M.S.O. 9s. 6d.

NEW YEAR HONOURS

It will give great pleasure to members of the B.M.A. that Professor A. P. Thomson has received the honour of knighthood during his year of Presidency of the Association. The vigour and efficiency of his work during the Annual Meeting at Birmingham last summer impressed all those who attended. The Birmingham Medical School owes much to him. After a brilliant career there as a medical student he qualified in 1915 and then served in the R.A.M.C. during the first world war, winning the M.C. and the Croix de Guerre. Appointed an honorary physician to the General Hospital at Birmingham in 1919, he is now consulting physician to the United Hospitals, and in the recent developments of the hospital services of his great city he has played a leading part. In the University of Birmingham he is professor of therapeutics and has been dean of the faculty of medicine since the death of Sir Leonard Parsons in 1951.

Two other medical men are knighted. Dr. A. W. Morrow is honorary physician at the Royal Prince Alfred Hospital, Sydney, and lecturer in therapeutics at the University of Sydney. During the second world war he gave distinguished service as a colonel in the A.A.M.C., being awarded the D.S.O. A Fellow of the Royal College of Physicians of London and of the Royal Australasian College of Physicians, he is this year's President of the New South Wales Branch of the B.M.A.

Dr. M. A. S. Margai, who also is made a knight, joins the small band of medical men who have become the leading ministers of their countries. He has been Premier of Sierra Leone since last summer. Born in Sierra Leone, he graduated in medicine at the University of Durham in 1926, and after attaining the rank of senior medical officer in the medical service of his own country he founded and became the leader of the People's Party, the first party to form a Government under the new constitution.

Members of the medical profession will be pleased to see that Professor A. W. G. Ewing has been honoured with a knighthood. Director of the department of education of the deaf at the University of Manchester, he and his wife, Dr. Irene Ewing, are international authorities on the education of deaf children and on methods of diagnosing defects of hearing in the very young. Professor Ewing is a member of two committees of the Medical Research Council, and the books he has written are standard works in the English-speaking world. An honour which will give special pleasure to those concerned with medical education in London is the knighthood conferred on Dr. D. W. Logan, principal of the University of London. Dr. Logan's work for the improvement of the London medical schools has been indefatigable.

Drug Treatment of Disease

DRUG TREATMENT OF CHRONIC BRONCHITIS

BY

J. G. SCADDING, M.D., F.R.C.P.

Physician, Brompton Hospital; Director of Studies, Institute of Diseases of the Chest; Physician, Postgraduate Medical School of London

The word "bronchitis" should correctly be applied to a disease characterized by inflammation of the bronchi. It is used accurately in this sense when applied to those conditions usually described as acute bronchitis, in which, often as a direct or indirect result of a respiratory virus infection, inflammatory changes spread down from the upper respiratory tract to the bronchi. In the condition usually described as chronic bronchitis, so common in Great Britain, it is at least doubtful whether the basic abnormality is essentially inflammatory in nature, even though the acute exacerbations of infective origin which commonly punctuate its course cause inflammatory changes leading to permanent damage of the lungs. In such episodes acute inflammation at bronchiolar level may result in purulent bronchiolitis, foci of pneumonia, and small abscesses. These may partly resolve, but may also lead to fibrotic occlusion of bronchioles, to scars due to organization of pneumonic foci, or to atelectasis beyond occluded bronchioles, and destructive emphysema. These changes result in the final clinical picture usually described in this country as "chronic bronchitis and emphysema." It is with the place of drugs in the management of this condition and of episodes of acute bronchitis that this article deals.

Some other forms of lung damage with emphysema, notably that associated with pneumoconiosis, present in their later stages problems of clinical management rather similar to those presented by chronic bronchitis and emphysema. The progressive bullous type of emphysema and "primary" emphysema affecting persons without previous bronchitis present some different therapeutic problems, which will not be discussed. Similarly, although wheezy dyspnoea due to reversible airway obstruction ("bronchospasm") may occur in chronic bronchitis and measures for relief of this symptom will be discussed, the special problems of the treatment of asthma are outside the scope of this article.

ACUTE BRONCHITIS

Acute bronchitis is most often a consequence of a viral infection, but commonly becomes complicated by added bacterial infection. Sometimes, especially in chronic bronchitic subjects, acute bronchitis appears to be precipitated by irritative rather than infective factors, the most frequent being exposure to a high concentration of atmospheric pollutants as in "smog." Many points in the treatment are common to acute bronchitis occurring in previously healthy persons and to acute exacerbations in chronic bronchitic subjects; in the latter, however, some special features require separate consideration.

Relieving Dry Cough

Certain symptomatic measures may be required. Although it is unwise to suppress a cough in chronic bronchitic subjects who have a constant excess of mucus in the respiratory tract, in the early stages of an acute tracheo-bronchitis in a previously healthy person there may be a troublesome dry cough which can legitimately be controlled by a suitable linctus. Codeine linctus *B.P.C.*, or, for more troublesome cough, methadone linctus, may be prescribed in the usual dose of 4 ml. At this stage, some patients will get relief from a steam inhalation with benzoin inhalation (vap. benzoin. *B.N.F.*) or menthol and benzoin inhalation *B.P.C.* (vap. menthol. et benzoin. *B.N.F.*). Later in the course of an acute bronchitis when expectoration starts, it may be helped by a suitable expectorant mixture such as the potassium iodide and ammonia mixture *B.P.C.*, or the sodium chloride compound mixture *B.P.C.*, taken in hot water (the Brompton Hospital "hot water medicine"). If wheezing dyspnoea indicative of bronchospasm is a feature, the antispasmodics mentioned below may be helpful, both in relieving this and in facilitating expectoration.

Cyanosis

Acute exacerbations of bronchitis in patients severely disabled with chronic bronchitis and emphysema present special problems. These patients become cyanosed from central anoxia and often have carbon-dioxide retention. Although oxygen is desirable to relieve the anoxia, it may result in such a rise of carbon dioxide tension that disturbances of consciousness and even coma may result. The best compromise in these patients is to give oxygen either in low concentration or intermittently. Nikethamide, given intravenously, is often helpful in stimulating the respiratory centres. Large doses are required, 5 to 10 ml. of the 25% solution being given slowly.

The special problems of the management of right ventricular failure and of the use of assisted respiration in such patients are outside the scope of this article.

Hypnotics

In bronchitic patients with impaired respiratory function, great caution is required in the use of hypnotics. Morphine and its analogues, and even barbiturates, are dangerous, and paraldehyde is probably the best hypnotic in a difficult case. It may be given as paraldehyde draught *B.P.C.*, 1½ fl. oz. (45 ml.), containing 60 minims (4 ml.) of paraldehyde.

Antibiotics

In both groups the question of the use of antibiotics against the bacterial infection arises. In a mild case of simple acute bronchitis it is reasonable to wait a day or so to see whether a phase of bacterial infection evidenced by a purulent sputum supervenes before starting antibacterial drugs. For chronic bronchitic subjects and for patients with more severe simple acute bronchitis it is probably wise to start treatment with a suitable antibiotic at the beginning, in the belief that, even though bacterial infection has not yet occurred,

the prophylaxis of such infection by suitable antibacterial drugs is likely to be beneficial.

The two common bacterial pathogens in bronchitis are *Haemophilus influenzae* and pneumococcus. Although the prevalence of these varies from time to time, in general it appears to be *H. influenzae* which is the most frequent pathogen. Nevertheless, if the patient is not gravely ill, it is reasonable to treat him for 24 hours or so as for a pneumococcal infection with penicillin, since the pneumococcus is susceptible to relatively small doses of this antibiotic and does not become resistant. But it is as well to treat more severely ill patients from the beginning as for *H. influenzae* infection. A combination of penicillin 500,000 units and streptomycin 1 g. twice daily is usually effective against *H. influenzae*, and can be continued for 5 days in most cases without ill effects. In older patients there is slight risk of vestibular toxicity from the streptomycin, but this is unlikely to develop within such a short period of administration. Caution is necessary also in patients who have renal damage. If there is nitrogen retention with a raised blood urea, streptomycin will also be retained and the customary dosage may lead to toxic levels in the blood. It is therefore better in such patients to use the alternative method of treatment by tetracycline 0.5 g. 3 or 4 times a day.

In a few patients *H. influenzae* infection may be resistant to either of these regimes. Then, if the sputum remains purulent, indicating the probability of continued lung damage at and beyond bronchiolar level, the use of chloramphenicol is justified in spite of the slight risk of a blood dyscrasia. In an acute case 0.5 g. 4 times a day is appropriate.

Usually there is little practical advantage to be gained from bacteriological studies in acute exacerbations, but the occasional case arises in which information derived from culture of sputum taken before antibacterial treatment begins may be valuable—e.g., in occasional cases a staphylococcus may be responsible. Therefore, if facilities are available it is advantageous to send a specimen of sputum to the laboratory for bacteriological examination before starting antibacterial drugs.

Whatever antibacterial treatment is given in an acute case of bronchitis, full dosage is unlikely to be required for more than 5 days. If at the end of this time the sputum has become clear and mucoid and the patient is not a known chronic bronchitic subject, the treatment can safely be discontinued. In some chronic bronchitic subjects, however, it may be wise to continue for some time after an acute attack with smaller doses of a broad-spectrum antibiotic, as will be discussed below.

CHRONIC BRONCHITIS AND EMPHYSEMA

In the management of chronic bronchitis and the progressive emphysema which eventually accompanies it, two groups of drugs are useful, the antispasmodics and antibacterial agents. The purpose of the antispasmodics is to relieve reversible airway obstruction, usually at bronchiolar level.

Antispasmodics

Some of the antispasmodic drugs are best given as occasion arises to deal with actual or expected bronchospasm. Among these are ephedrine, isoprenaline, and other sympathomimetic drugs. It is a common experience that, if these are taken regularly, they tend to lose their effectiveness. Many chronic bronchitics wake in the morning with wheezy dyspnoea. They can take ephedrine ½ gr. (30 mg.) or isoprenaline 20 mg. on waking. The patient should be advised to have it ready at his bedside. Ephedrine tablets are swallowed in the usual way, while isoprenaline tablets are allowed to dissolve under the tongue. Similarly, these drugs may be taken before any activity which is known to be likely to bring on wheezing and dyspnoea—e.g., some necessary exertion or going out into the cold air.

The limiting factor to the dosage of both these drugs is usually their effect on the cardiovascular system, patients complaining of palpitations, tachycardia, and sometimes of a feeling of "goose-flesh" from cutaneous vasoconstriction. If these side-effects are not severe, the dose of ephedrine may be increased to 1 gr. (65 mg.). Another untoward effect sometimes caused by these drugs, particularly ephedrine, is that they may cause difficulty in micturition in middle-aged and older men with prostatic enlargement.

Inhalation of 1% isoprenaline from a nebulizer is helpful to some patients, and its use should be timed similarly to that of the oral sympathomimetic drugs.

Theophylline

The various preparations of theophylline suitable for oral administration are probably best given in regular dosage. Of these, choline theophyllinate, 200 mg. thrice a day, is usually well tolerated and may be helpful. The maximum dosage is determined by gastric tolerance, and for patients who tolerate the drug well the dose may be increased to 400 mg. Antispasmodic drugs of both the sympathomimetic and the theophylline groups have a cerebral stimulant effect. For this reason several proprietary antispasmodic preparations contain subhypnotic doses of barbiturates. Such are "franol," which contains phenobarbitone 1/8 gr. (8 mg.) with ephedrine 3/20 gr. (10 mg.) and theophylline 2 gr. (130 mg.); "tedral," of similar composition but with a larger content (3/8 gr. (24 mg.)) of ephedrine; and "amesec," which contains aminophylline 130 mg., ephedrine hydrochloride 25 mg., and amylobarbitone 25 mg. These may be helpful during the day to those patients who experience feelings of anxiety and apprehension after taking the antispasmodic drugs alone, and sometimes to those who are troubled by palpitations. If a hypnotic is required at night, it is best to give an effective dose of a hypnotic drug separately from the antispasmodic.

Secondary Infection

The control of secondary bacterial infection in chronic bronchitics by long-term administration of small doses of broad-spectrum antibiotics has received much attention recently. Such treatment is expensive and carries several risks. The emergence of resistant strains of bacteria, especially staphylococci, is one of them. These organisms are potentially dangerous not only to the patient but also to people he meets, to whom he may pass them on. Fortunately, the pneumococcus almost never and *H. influenzae* only rarely become resistant to antibacterial drugs.

Some patients will develop gastro-intestinal symptoms, particularly diarrhoea, while receiving these drugs, presumably from alteration of the normal bacterial flora of the alimentary tract; but staphylococcal enterocolitis, the most extreme and dangerous variety of this, appears to be rare in bronchitic patients receiving the small doses customarily used for prophylaxis. Against these disadvantages must be set the diminution of

periods of disability and absence from work occasioned by acute inflammatory exacerbations of bacterial origin which many chronic bronchitics suffer during the winter months.

It is probably not possible to generalize about this form of treatment, since the causes of disability in chronic bronchitic subjects vary from patient to patient. Some have their principal disability from persistent dyspnoea due to emphysema and others from persistent bronchospasm of non-inflammatory origin; these will not benefit from long-term antibacterial treatment.

Patients who are usually fit to continue with normal activities and have a non-purulent sputum but suffer a few acute exacerbations each winter are probably best managed by treating each episode promptly, by the administration of tetracycline at the beginning of even apparently trivial upper respiratory infections. Patients whose sputum without treatment is consistently purulent but becomes mucoid and can be maintained so by the administration of a suitable antibiotic, or who have very frequent exacerbations of bacterial infection, may be tried on tetracycline in small doses during the season of the year when acute respiratory infections are frequent. For patients whose sputum is initially mucoid, 0.25 g. twice a day may be sufficient; for those whose sputum is initially purulent, somewhat larger doses should be given at the beginning, say 0.25 g. 4 times a day, the dosage being reduced steadily to the smallest level which maintains a mucoid sputum. If the sputum remains purulent in spite of treatment, it is unlikely that the treatment is doing any good and it should be stopped. For those who benefit, the antibiotic should be continued during the season of prevalence of respiratory infections, say from the beginning of November until the end of March or the middle of April. They probably constitute a minority of the sufferers from this very common disease.

It must be emphasized that this article deals with drug treatment and does not touch upon other important aspects of the management of chronic bronchitis, such as general regime, the avoidance of smoking, and physiotherapeutic methods.

A DECADE OF ANTI-INFLAMMATORY STEROIDS

[FROM A SPECIAL CORRESPONDENT]

Ten years ago cortisone was first given to a patient suffering from rheumatoid arthritis. To mark this occasion a conference was held at the New York Academy of Science on December 15 and 16 to survey "A Decade of Anti-inflammatory Steroids from Cortisone to Dexamethasone." This was a valuable opportunity to review the clinical usefulness of various corticosteroids in a wide variety of diseases, and to assess the benefits of the modifications chemists have made to the molecular structure of cortisone and hydrocortisone in their endeavours to evolve more potent anti-inflammatory compounds with yet fewer side-effects.

Cortisone and Fluorohydrocortisone

The first two sessions of the conference were devoted to the chemical, biological, and metabolic properties of the anti-inflammatory steroids, and were under the chairmanship of Dr. JOSEPH BUNIM and Dr. EDWARD C. KENDALL, whose contributions to the synthesis of cortisone have been recognized in a Nobel prize. Although the mechanism of its anti-inflammatory action remains undiscovered and despite little being known about the relationships of chemical structure to antiphlogistic action, cortisone might still be the steroid of choice were it not for a number of undesirable side-effects. In large dosage cortisone causes retention of salt and water, inducing in some patients oedema and hypertension. It also has an anti-anabolic effect on protein synthesis, and by depressing the normal maintenance and repair of proteinous tissue, particularly bone, may after prolonged administration cause osteoporosis and pathological fractures of vertebrae. It also influences carbohydrate metabolism and in high dosage may induce a diabetic state which is usually reversible on withdrawing treatment.

It was soon appreciated, however, that these different properties of cortisone might be modified by altering the structure of the steroid molecule. The first major change came in 1952 when a fluorine atom was introduced at the C-9 position. This disproportionately enhanced the sodium-retaining property of the compound, and made fluorohydrocortisone valueless as an anti-inflammatory substance except in the topical treatment of skin diseases. Nevertheless its intense action on sodium metabolism has given it a small but important place in the treatment of Addison's disease and adrenalectomized patients, where it has displaced deoxycortone because it is effective by mouth.

Prednisone and Prednisolone

The second major change, and one that heightened the anti-inflammatory potency of the compound, came in 1954 with the unsaturation of the bond between the first and second carbon atoms in the steroid molecule. The resulting delta compounds (prednisone and prednisolone) proved to have an anti-inflammatory effect some four times as great as cortisone or hydrocortisone on a weight-for-weight basis without a proportionate increase in sodium-retaining activity. Although this reduced the liability to oedema or hypertension, many investigators reported that this benefit had to be balanced against an apparently greater tendency to produce peptic ulceration. The development of gastric ulcers had been observed in patients treated with cortisone, but with the delta compounds this complication of treatment seemed more common, and not infrequently the ulcer was symptomatically silent until it perforated or bled.

Dr. GORDON TOMKINS, of the National Institute of Arthritis and Metabolic Disease at Bethesda, explained that cortisone was largely metabolized in the liver, and that the rate of degradation depended on saturation of the 4–5 double bond by two separate enzyme systems—one a series of soluble reductases, which catalyse the production of 5β-dihydrosteroids, and a microsomal enzyme which produces 5α-dihydro compounds. The additional double bond in prednisone and prednisolone between the first and second carbon atoms appeared to increase the *in vivo* stability of the molecule, and this gave it an enhanced anti-inflammatory potency.

These delta compounds have therefore been the starting-point in the search during the last four years for other steroids with greater anti-inflammatory effect but less undesirable side-effects. Such is the structure of the steroid molecule that possible permutations and combinations are almost innumerable, and each new compound synthesized by the chemist has had to be submitted to a long series of exacting biological tests before clinical trials are possible. Only a very few of the many compounds made have shown sufficient promise to merit application in human diseases. Furthermore, since so little is known of the mechanism by which corticosteroids produce their beneficial effect at cellular level, it has proved impossible to predict with any accuracy what will be the effect of adding, for example, a methyl group at any particular location in the steroid molecule.

Triamcinalone and Dexamethasone

The next compound to achieve some clinical importance was triamcinalone, which was a prednisolone molecule with a fluorine atom at the C-9 position and hydroxylation of the

16th carbon atom. The addition of the –OH group completely reversed the sodium-retaining properties imparted by the fluorine atom, and triamcinalone was strikingly free of any tendency to produce oedema or hypertension. Weight for weight its anti-inflammatory action was much the same as prednisolone, and it would have constituted a therapeutic advance were it not for its liability to induce certain side-effects—anorexia, nausea, weight loss, and severe muscle weakness (particularly in the legs)—which have not been encountered with other synthetic compounds.

The latest corticosteroid to be introduced is dexamethasone, which is prednisolone with a fluorine atom at the C-9 position. This compound is also devoid of sodium-retaining properties but has a much greater anti-inflammatory effect than triamcinalone, being seven times more potent than prednisolone on a weight basis and some 30 times more potent than cortisone or hydrocortisone. It is therefore the most potent anti-inflammatory substance available. The usual dose required to control a patient with rheumatoid arthritis is 1.5 mg. daily, with a range from 0.75 to 2.5 mg. a day. It is perhaps too soon to assess its liability to produce side-effects. There is some evidence that it causes less disturbance of carbohydrate metabolism, but it may induce weight gain, mooning of the face, and abdominal distension.

Value in Rheumatoid Arthritis

The remaining sessions of the conference were devoted to the clinical value of steroids in general, and dexamethasone in particular, in the treatment of some of the common disorders and were under the chairmanship of Dr. RUSSELL L. CECIL and Dr. PHILIP S. HENCH, another Nobel laureate for his pioneer work in the treatment of rheumatoid arthritis with cortisone.

Dr. EDWARD BOLAND, of California, and Dr. OSWALD SAVAGE, of London, who reported the experience of the West London Hospital, were in close agreement concerning the indications for steroid treatment in rheumatoid arthritis and the benefits obtained by the patient. Dr. BOLAND had with dexamethasone achieved adequate control of symptoms in 80% of his patients in a dose ranging from 1 to 2.5 mg. daily. Side-effects occurred in about the same frequency as with prednisone, some patients showing a marked increase in appetite and weight with abdominal distension.

Dr. SAVAGE reported that the degree of improvement with dexamethasone was similar to that achieved with prednisolone, and there was little difference in the incidence of side-effects. These were in the main not of great importance and should not be over-emphasized. Despite the three most important drawbacks to steroid treatment of any kind—the tendency to temporary adrenal insufficiency after stopping treatment, the liability to peptic ulceration, and the possibility of osteoporosis developing—he was uncompromising in the value of this form of treatment which had allowed previously crippled patients to return to work and brought a substantial measure of relief to many other less seriously affected patients. Awareness of previous steroid therapy had allowed major and minor surgical procedures to be carried out without risk under cover of increased steroid dosage during the operative period, and no difficulties from infection or inadequate wound healing had been encountered. Osteoporosis was a problem, particularly in older patients on prolonged treatment: it was important to use the smallest dose of corticosteroid possible and to achieve a worthwhile degree of symptomatic relief but not necessarily complete freedom from symptoms.

Peptic Ulceration

The significance and incidence of peptic ulceration was mentioned by many speakers. Dr. BOLAND reported that all the compounds he had used were potentially ulcerogenic and the incidence in rheumatoid arthritis patients was about 8.6%. In some instances, however, the ulcers were clinically silent and discovered only during routine *x*-ray studies. He advocated the concurrent administration of antacids during steroid therapy. Dr. SAVAGE noted that peptic ulcers were commoner in patients with rheumatoid arthritis than in those with other diseases treated with corticosteroids, and certainly workers in other fields such as Dr. DANIEL M. GORDON, who used large doses of dexamethasone for the treatment of eye diseases, had experienced no difficulty from this side-effect.

Dr. WALTER PALMER was not even convinced from statistical data that there was any causal relationship between steroid therapy and peptic ulceration. In his wide experience of ulcerative colitis, peptic ulceration and dyspepsia were as common in control patients as those treated with steroids, and he also pointed out that perforation of the colon in this disease was sometimes more common in patients not having anti-inflammatory compounds as in those who were.

Blood Diseases and Nephrosis

The great value of steroid therapy in blood diseases was described by Dr. WILLIAM DAMESHEK as revolutionary. Corticosteroids were essential in the treatment of acute leukaemia and lymphatic leukaemia, auto-immune haemolytic anaemias, and idiopathic thrombocytopenic purpura, often making splenectomy unnecessary. They also played an important part in reducing host rejection in the present attempts to achieve successful bone-marrow transplantation in the treatment of aplastic anaemia and leukaemia.

Dr. CONRAD RILEY reviewed his long experience of nephrosis in children. He showed not only that corticosteroids produced symptomatic improvement, but that prolonged treatment with the newer compounds significantly increased the survival time and reduced the frequency of relapse. The great value of short-term, and in some instances continuous, treatment with steroids in allergic conditions and skin diseases was discussed by Drs. BRAM ROSE and SAMUEL C. BUKANTZ and by Drs. VICTOR H. WITTEN and LEON GOLDMAN.

The impressions left at the end of the conference were several. We must not forget the very real benefits that corticosteroids have brought to clinical medicine. Dexamethasone is yet another step along the difficult road which must ultimately lead to the ideal anti-inflammatory steroid. In the United States there is a greater awareness of the clinical usefulness of corticosteroids, and, being more familiar with their application, the practitioner is less fearful of side-effects. Finally, we must not slacken our search for the mechanism of how these compounds work; the answer to this may well give the answer to many other problems.

MEDICAL NEW YEAR HONOURS

The names of the following members of the medical profession were included in the New Year Honours List published in the *London Gazette* on January 1.

Knighthood

ARTHUR PEREGRINE THOMSON, *M.C.*, M.D., F.R.C.P. President of the British Medical Association. Professor of Therapeutics and Dean of the Medical School in the University of Birmingham.

MILTON AUGUSTUS STRIEBY MARGAI, M.B.E., M.B., B.S. Premier of Sierra Leone.

ARTHUR WILLIAM MORROW, D.S.O., E.D., M.B., B.S., F.R.C.P., F.R.A.C.P. Honorary Physician, Royal Prince Alfred Hospital, Sydney. For services to medicine.

C.B. (Military Division)

ROLAND ANTONY BENNETT, M.D., F.R.C.P.Ed. Major-General, late R.A.M.C. Honorary Physician to the Queen. Consulting Physician to the Army.

C.M.G.

NORMAN LACE CORKILL, M.D. Health Adviser, Aden Protectorate.

C.B.E. (Military Division)

CHARLES BOYD NICHOLSON, M.B., B.S., D.L.O. Surgeon Captain, R.N.(ret.).

ALISTAIR GORDON DONALD WHYTE, M.B.E., M.B., Ch.B., F.R.C.S.Ed. Colonel, late R.A.M.C.

C.B.E. (Civil Division)

MURIEL EMMA BELL, M.D., F.R.S.N.Z. Nutritionist to the Department of Health and Supervisor of the Nutrition Research Department of the Medical Research Council of New Zealand.

BRICE RICHARD CLARKE, *M.C.*, M.D. Consulting Chest Physician, Northern Ireland Tuberculosis Authority.

ARTHUR RICHARDS CULLEY, M.D., D.P.H. Principal Medical Officer, Welsh Board of Health.

IVAN DE BURGH DALY, M.D., F.R.C.P., F.R.S., F.R.S.Ed. Lately Director, Institute of Animal Physiology, Agricultural Research Council, Babraham, Cambridge.

MICHAEL GELFAND, O.B.E., M.D., F.R.C.P., D.P.H., D.M.R. Physician to Salisbury Hospital, Southern Rhodesia. For services to medicine in the Federation of Rhodesia and Nyasaland.

JOHN ALEXANDER JAMES, O.B.E., M.B., Ch.M., F.R.C.S., of Braddon, Australian Capital Territory. For services to the community.

GEORGE CARMICHAEL KELLY, M.D., D.P.H. Honorary Physician to the Queen. Senior Administrative Medical Officer, South-Western Regional Hospital Board.

ALAN BRUCE LILLEY, M.B., Ch.M. Formerly Chairman of the Hospitals Commission, and at present Medical Director of the Cancer Council, New South Wales.

EDWARD ERIC POCHIN, M.D., F.R.C.P. Director, Department of Clinical Research, University College Hospital Medical School, Medical Research Council.

KENNETH ROBSON, M.D., F.R.C.P. Civil Consultant in Medicine to the Royal Air Force.

O.B.E. (Military Division)

ARTHUR FAWCETT MILLER BARRON, V.R.D., M.D., F.R.C.S.Ed. Surgeon Commander, R.N.V.R.(ret.).

GEORGE LEE RITCHIE, M.B., Ch.B., D.P.H., D.T.M.&H., D.I.H. Lieutenant-Colonel, R.A.M.C.

O.B.E. (Civil Division)

EDWARD GORDON ANDERSON, M.B., Ch.B. Chairman, Birmingham No. 2 Medical Board.

MAURICE AILWYN BYER, M.B., Ch.B. Director of Medical Services, Barbados.

DAVID ALEXANDER CANNON, M.B., Ch.B., D.T.M.&H. Senior Specialist (Pathologist), Federation of Nigeria.

CECIL JOHN CELLAN-JONES, T.D., M.D., F.R.C.S.Ed. Chairman, Swansea Disablement Advisory Committee.

WILLIAM JOHN LYON DEAN, M.B., Ch.B., J.P. Lately Provost of Lossiemouth.

PETER ROYLANCE DELAMOTHE, M.B., B.S. In recognition of services rendered to the town of Bowen, Queensland.

JOHN WILSON KYLE, M.B., B.Ch. For services to Rugby football in Northern Ireland.

IAN ALEXANDER MCGREGOR, L.R.C.P.&S.Ed., D.T.M.&H. Director of Medical Research Council Laboratories, Fajara, Gambia.

PHILIP WHITESIDE MACLAGAN, *M.C.*, M.D. General medical practitioner and medical officer of health, Berwick.

ISIDORE ROWLAND ROSIN, M.D., F.R.C.S.Ed. A medical practitioner of Salisbury, Southern Rhodesia. For services to medicine in the Federation of Rhodesia and Nyasaland.

JOHN ELVIN RUSBY, *M.C.*, T.D., L.M.S.S.A., J.P. General medical practitioner, Leeds.

CYRIL JOSEPH TONKIN, M.B., B.S., F.P.S., of Toorak, Victoria. A prominent physician. For many years Lecturer in Pharmaceutical Botany, Victoria College of Pharmacy.

ANNIE DORIS WILSON, M.B., Ch.B. Physician, Edinburgh Medical Missionary Society Hospital, Nazareth.

M.B.E. (Military Division)

BRIAN DEVLIN, M.B., Ch.B., D.P.H., D.T.M.&H. Major, R.A.M.C.

HERBERT SAMUEL GAVOURIN, M.B., B.S., M.R.C.O.G. Major, R.A.M.C.

JOHN FRANCIS HICKEY, L.R.C.P.&S.I. Late Captain, R.A.M.C.

M.B.E. (Civil Division)

JOSEPH ANDREW ARRATTA, M.B. A medical practitioner of Muttaburra, Queensland.

CLARENCE ERIC STANLEY BAILEY, M.B., Ch.B., D.P.H., D.T.M.&H. Medical Superintendent, Holberton Hospital, Antigua, Leeward Islands.

JOAN CATHERINE CLATWORTHY, M.B., B.S. For public services in the Western Region, Nigeria

CHARLES GIBBONS SEYMOUR, M.R.C.S., L.R.C.P., D.T.M.&H. Major, I.M.S.(ret.). Member, National Service Medical Board, Southampton.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Ferroids (Riker).—Each tablet contains iron aminoates (iron chelated with a complex of amino-acids) 350 mg. (equivalent to 35 mg. elemental iron) and aneurin hydrochloride 1 mg.

Plesmet Tablets (Coates and Cooper).—Each tablet contains ferrous aminoacetosulphate (equivalent to 30 mg. ferrous iron) and aneurin hydrochloride 1 mg.

These preparations contain iron chelated with amino-acids. The word chelate is derived from the Greek " chele," meaning " claw." Chelates are ring structures formed between metallic ions and the molecules of an organic substance known as a chelating agent to form a stable compound. Where chelating bonds are strong, the compound in solution does not show the typical reactions for the presence of the metal. It is believed that the advantages gained from chelation, in the case of iron compounds, are greater stability of the iron compound in the stomach with a lower incidence of gastric discomfort, and the possibility of an increased absorption and utilization of iron from the intestines. Experience with chelated iron preparations is still rather limited, and opinions on their value are conflicting. They are probably as effective as most iron salts in the treatment of iron-deficiency anaemia, though they are more expensive than some. Gastro-intestinal side-effects of orally administered iron compounds are apt to be more closely dependent on the dose of elemental iron than on the form in which it is prescribed, and it is too early to give a firm opinion on whether these side-effects are less severe on chelated iron than on the simpler iron salts. Some observers have reported that they are.

N.H.S. basic price: ferroids, 100 tabs., 8s. 8d.; plesmet, 100 tabs., 2s. 8d.

Incidal (Farbenfabriken Bayer A.G. (Distributors: Levmedic)).—This is a new antihistamine preparation which is reported to cause relatively little sedation. It is the naphthalene-1:5-disulphonic acid salt of 3-N-methyl-9-benzyl-tetrahydro-γ-carboline and is chemically more complex than most of the known antihistamine drugs. It is supplied in 50-mg. tablets, and the dose for adults is 2–6 tablets a day, taken every 4–5 hours.

N.H.S. basic price : 10 tabs., 3s. 6d.

Staphylococcus toxoid (Glaxo).

Staphylococcus toxoid (Parke, Davis).

These are prepared by converting a potent toxin of *Staphylococcus aureus* into a " toxoid " by the addition of formalin. They are intended for the treatment of chronic staphylococcal infections such as recurrent boils, pustular acne, chronic and subacute osteomyelitis, nasal infections, blepharitis, and conjunctivitis. It is usual to begin treatment with the subcutaneous injection of 0.1 ml. of the solution, increasing the dose by 0.1 ml. at weekly intervals to reach the maximal dose of 1 ml. Four to six doses of 1 ml. are given at weekly intervals thereafter. It is also suggested that a similar course can be repeated where necessary.

There is some doubt about the effectiveness of previous preparations of staphylococcal toxoid. In the writer's experience it is questionable whether a simple toxoid is of value except in patients showing individual hypersensitivity to staphylococcal toxins. It remains to be seen whether the newer preparations will prove to be more efficacious.

N.H.S. basic price: Glaxo toxoid 5-ml. phial, 3s. 9d.; Parke, Davis toxoid, eight 1-ml. ampoules of " strong " toxoid in graduated doses, 16s. 10½d., and phials containing other doses also available.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Medical Services Review Committee

SIR,—In your issue of December 6 (p. 1401) you kindly published the names of the members of the Medical Services Review Committee which has been set up by the Royal Colleges and Scottish Royal Medical Corporations, the Society of Medical Officers of Health, the College of General Practitioners, and the British Medical Association to review the provision of medical services to the public, and their organization, in the light of 10 years' experience of the N.H.S.

From conversations which I and members of my committee have had with other members of the profession, it appears that there may be some misunderstanding as to the purpose and scope of our inquiry, and I would like to take this opportunity of emphasizing that we do not regard ourselves as having been appointed merely to carry out yet another investigation into the operation of the National Health Service.

Our terms of reference make it clear that we have to examine the medical services in this country in the light of experience of the N.H.S. Indeed, it would be wrong to pretend that any worthwhile study of the work of the profession could ignore the impact made upon it by the N.H.S. We consider, however, that our terms of reference are much wider and require us to review the practice of medicine in all its aspects and in all fields, clinical, social, and preventive, both within and outside the N.H.S.

We shall try to find out what advantages, and what disadvantages, the changing pattern of medical practice has brought to the patient, the community, and the doctor, and we hope our inquiry will be fruitful in indicating the lines on which future development should be planned.

We recognize the magnitude of our task, and to complete it successfully we shall need the co-operation of the profession and the public. At an early date we shall therefore be inviting evidence from professional bodies and from organizations representing various sections of the community, but we shall always be pleased to receive the views of any organized body or individual touching the subject of our inquiry.—I am, etc.,

B.M.A. House,
Tavistock Square,
London, W.C.1.

ARTHUR PORRITT,
Chairman,
Medical Services Review Committee.

Potassium Perchlorate Sensitivity

SIR,—Dr. B. J. Fairhurst and Dr. Ann L. M. Hollingworth (*Journal*, December 20, p. 1531) report a case of potassium perchlorate sensitivity. We have now used potassium perchlorate in the treatment of a large series of cases of thyrotoxicosis and have compared its toxicity with that of both methyl thiouracil and carbimazole. The Table shows our results to date.

All the skin rashes produced by potassium perchlorate, except one, occurred in patients who were receiving 2,000 mg. daily. The rash produced by the drug was maculo-papular in nature and confined to the extremities, except in one patient in whom the rash was generalized. He resembled the case reported by Drs. Fairhurst and Hollingworth in that there was an associated systemic upset with pyrexia and marked desquamation. In three of the six cases the rash subsided although the administration of the drug was continued.

We should like to draw attention to the case of agranulocytosis produced by perchlorate, since this complication has not been previously described.

Drug:	Methyl Thiouracil	Carbimazole	Potassium Perchlorate		Total
Dosage	600 mg. daily for 2 Weeks, then 300 mg. Daily	60 mg. Daily for 2 Weeks, then 30 mg. Daily	600–1,000 gm.	1,500–2,000 mg.	
No. of cases ..	151	70	154	50	*204*
Toxic effect:					
Skin rashes ..	5	4	1	5	6
Nausea ..	—	1	3	2	*5*
Drug fever ..	2	—	—	—	—
Agranulocytosis	2	2	—	1	*1*
Thrombocytopenia ..	1	—	—	—	—

The patient, a young female, was treated with perchlorate in doses of 500 mg. three times daily. During the third week of treatment she developed a sore throat and pyrexia with generalized muscle pain. Blood examination revealed a polymorphonuclear leucocyte count of 750/c.mm., but the other blood findings were normal and the bone marrow histology showed no evidence of a maturation defect of the white cell series. After the drug was stopped there was a rapid rise of the leucocyte count to normal levels. The patient had not been receiving any other drugs and the evidence points to perchlorate as the causative agent.

There was no statistically significant difference in the incidence of either skin rashes or blood dyscrasias produced by perchlorate, methyl thiouracil, or carbimazole. The toxic effects during treatment with potassium perchlorate in doses of 1,000 mg. daily or less were, however, significantly less frequent than with larger doses of the drug or with either methyl thiouracil or carbimazole. Thyrotoxicosis is as quickly and as completely controlled by 1,000 mg. daily of perchlorate as by methyl thiouracil or carbimazole in the doses shown in the table. Although, like all its predecessors, potassium perchlorate has not fulfilled its initial promise, our results suggest that, provided a dose of 1,000 mg. daily is not exceeded, it is both effective and relatively free from serious side-effects.—We are, etc.,

Department of Medicine,
University of Glasgow.

J. CROOKS.
E. J. WAYNE.

SIR,—The report of potassium perchlorate sensitivity by Dr. B. J. Fairhurst and Dr. Ann L. M. Hollingworth (*Journal*, December 20, p. 1531) is of considerable interest, as we have recently observed a similar case in which there was difficulty in both diagnosis and treatment. The details of this patient may therefore also be of interest.

Female, aged 15. Earlier this year, at another hospital, the diagnosis of thyrotoxicosis had been made and the girl was treated with methyl thiouracil. Because of enlargement of the gland, however, and the appearance of signs of hypothyroidism, including serum cholesterol of 444 mg.%, it was suggested that all therapy be stopped and the girl kept under observation. She did not return to that hospital and was seen at our clinic on October 24, when she was undoubtedly severely thyrotoxic. Treatment with potassium perchlorate, 400 mg. thrice daily, was started. On November 6 her own practitioner prescribed a sedative mixture containing phenobarbitone. She developed a skin

rash and diarrhoea on November 12 and all drugs were discontinued on November 15. As there had been no improvement, she was admitted to hospital on November 18.

On examination she was grossly thyrotoxic, being extremely restless and excitable. The pulse rate was 120 per minute. The whole body was covered with a profuse, red maculo-papular rash. Some of the papules were follicular, but there was no purpura. The mouth and throat were erythematous, with numerous small areas of ulceration. No lymphadenopathy or splenomegaly was present. There was no pyrexia on admission. The white cell count was 1,700/c.mm., 47% being neutrophils (800/c.mm.). Treatment with promethazine hydrochloride, 50 mg. twice daily, and A.C.T.H. gel, 50 units daily, produced no change in the rash, but the mouth lesions did improve rapidly with cortisone hemisuccinate "linguets." She remained grossly thyrotoxic despite the administration of Lugol's iodine, 2 minims (0.1 ml.) four-hourly. The diarrhoea continued, stool culture being negative. On the fifth day after admission a pyrexia of 101° F. (38.3° C.) developed and continued between 101° and 103° F. (38.3°–39.4° C.), although no abnormality in the chest or urine was found. Crystalline penicillin was given. Her thyrotoxic state was unaffected by oral reserpine, 0.25 mg. 6-hourly, but some temporary improvement appeared to follow chlorpromazine, 25 mg. intramuscularly. On the seventh day the rash started to desquamate. The following day her temperature reached 104.8° F. (40.45° C.). Evidence of consolidation was now found at her left lung base. Following tetracycline, 250 mg. 4-hourly, the pyrexia subsided. Intramuscular reserpine, 0.25 mg. 6-hourly, was also started, and there was a gradual improvement in the thyrotoxic state, her pulse rate, which had risen to 140 per minute even while asleep, settling to 96 per minute. On the fourteenth day, oral reserpine was substituted. Her general condition remained satisfactory, but it was noted that her pulse rate again increased to 120 per minute. The desquamation gradually disappeared, the skin returning to normal.

With a fairly extensive use in this department of potassium perchlorate (in daily dosage of 600–1,200 mg.) in the treatment of thyrotoxicosis during the past 18 months, the only toxic effects of this drug observed have been transient gastro-intestinal upsets and two mild skin rashes. In this patient, therefore, we felt that the sensitivity reaction was more likely to have resulted from the barbiturate therapy. Although thyrotoxicosis might have been partly responsible for the diarrhoea, it was difficult to explain the leucopenia and mouth lesions. It was therefore thought that these might well have been caused by the potassium perchlorate, and indeed that this drug might have been responsible for the whole sensitivity reaction. An intradermal skin test with potassium perchlorate solution gave a rapidly positive erythematous reaction. The similarity of this case to that reported by Drs. Fairhurst and Hollingworth also suggests that the potassium perchlorate was indeed the sensitizing drug. The failure to respond to antihistamines and A.C.T.H. is surprising. This patient is also of interest, as she showed the value of intramuscular reserpine as part of the treatment of incipient or actual thyrotoxic crisis.—I am, etc.,

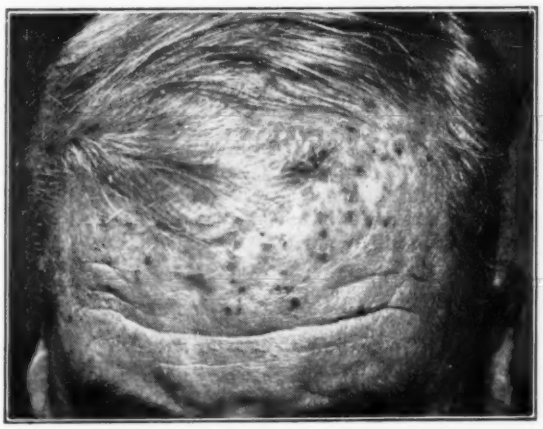
Department of Endocrinology, Glasgow Royal Infirmary. I. P. C. MURRAY.

Acne Necrotica due to Phenylbutazone

SIR,—I wish to report a case of acne necrotica due to phenylbutazone.

H. D., aged 52, an acetylene welder, was referred to the Skin Department of the Leeds General Infirmary by Professor S. J. Hartfall on January 20, 1958, with a rash on the forehead. He was being treated for osteoarthritis and had been on phenylbutazone, 200 mg. daily, for three weeks. Two weeks after beginning treatment, an irritable rash had appeared on the forehead near the hairline (see Fig.).

He was a stolid obese man who showed the typical excoriated papules and commencing varioliform scars of acne necrotica on the forehead. On stopping the phenylbutazone and using ung. sulphur. et acid. salicyl. 2%, the rash subsided. On resuming the drug the rash recurred. The drug was again stopped and no treatment was given;



the rash again disappeared and he remained clear for two months. He was then given one 200-mg. tablet of phenylbutazone daily. Previously he had taken two 100-mg. tablets. These tablets, being white and red respectively, are not readily identified by the patient as the same drug. When seen two weeks later there was no rash, but it recurred during the following week. On stopping the tablets it disappeared in another two weeks and has not recurred since.

This case is interesting in that acne necrotica is usually considered to be due to infection, psychological factors, or a combination of the two. I can find no reference in the literature to its occurrence as a drug eruption.

I wish to thank Dr. F. F. Hellier for his help in reporting this case.

—I am, etc.,

Adelaide, South Australia. G. A. HUNTER.

Hospital Sterilization

SIR,—As is noted in your leading article (*Journal*, December 27, p. 1582, para. 3) "Defects in Sterilization," hospital arrangements for treating soiled linen are often defective. Nurses may be expected to clean foul linen on the wards and dry it before dispatch to the laundry. Sometimes the linen is returned clean in the same basket as was used for sending it dirty to the laundry. In this hospital, on the suggestion of Dr. G. A. Lilly, of the Board of Control, in October, 1951, a satisfactory scheme was introduced, and the following instructions are issued to all wards:

LAUNDRY

Washing that is not foul, though it may be wet, is entered in the proper book, and sent to the laundry weekly.

Foul washing must be kept separately.

FOUL WASHING

Each article must be entered in the special book, when it is put in the proper bin.

Be careful to do this correctly to avoid further sorting of potentially infected material.

Put all *Foul Wash* in the coloured bins:

White linens and cottons in the white striped bin.
Coloured linens and cottons in the blue striped bin.
White woollens in the uniform white bin.
Coloured woollens in the uniform blue bin.

Enter each article as you put it in.

In fact, the bins have now been replaced by wheeled bedside containers, to which a notebook and pencil are attached, with coloured bags for foul linen; these bags are closed and transported to the laundry, where the contents are tipped straight into disinfectant.

The advantages of this scheme are that no handling of foul laundry takes place, except from the bedside to the bag, until it has been sterilized, and so the staff are saved from an unpleasant task with risk of infection. A theoretical disadvantage is that linen is not so thoroughly checked, but in practice this has not caused excessive losses.—I am, etc.,

The Central Hospital, Nr. Warwick. E. S. STERN.

Traumatic Fore-quarter Avulsion

SIR,—Apropos Mr. D. S. Pracy's interesting report of a traumatic fore-quarter avulsion (*Journal*, December 27, p. 1578), an early example of this formidable injury is illustrated by a copperplate* in William Cheselden's *The Anatomy of the Human Body*. The patient was a miller, Samuel Wood, whose arm was caught in a rope attached to the cogs of his mill. He was treated at St. Thomas's Hospital with superficial dressings only, lost little blood, and recovered without severe symptoms. The year was 1737.—I am, etc.,

General Hospital, Northampton. H. ELLIS.

. This copperplate was reproduced in our issue of October 16, 1948 (p. 722), where it illustrated a letter by Mr. J. Dudfield Rose drawing attention to the case of the miller.—ED., *B.M.J.*

Afibrinogenaemia after Transfusion

SIR,—Having read the comments of Dr. H. J. Friend and Surgeon Rear-Admiral S. G. Rainsford (*Journal*, December 27, 1958, p. 1592) on my recent article (*Journal*, November 15, p. 1201), I must say that I am in complete sympathy with any attempt to prevent the misuse of such a valuable and potentially dangerous material as donated blood. In my anxiety to avoid confusing the issue regarding the trigger mechanism of the afibrinogenaemia, which I have no doubt was the incompatible transfusion, I may have painted too rosy a picture of the patient's immediate post-operative condition. I can only say that her condition was not in any way unusual for a patient after a major surgical operation, but that in the opinion of those responsible blood transfusion was desirable.

Surgeon Rear-Admiral Rainsford raises a number of points regarding dextran. Although it is obvious that dextran played no part in the onset of the afibrinogenaemia, I feel that administration of any substance known to interfere in any way with the haemostatic processes was inadvisable. I consider that there is enough clinical evidence given in the papers I quoted on dextran to make me reluctant to order it in any condition associated with bleeding. Now that "large pool" plasma is no longer used and the risk of infective hepatitis from plasma is probably no greater than from blood, it might be debated whether there is still a need for unphysiological substitutes such as dextran in civilian hospital practice.—I am, etc.,

Victoria Infirmary, Glasgow, S.2. JAMES M. MOORE.

SIR,—The letters of Dr. H. J. Friend and Surgeon Rear-Admiral S. G. Rainsford (*Journal*, December 27, 1958, p. 1592) regarding the paper by Mr. James M. Moore (*Journal*, November 16, p. 1201) raise the question as to whether the blood given was really necessary. As one who is constantly faced with the problem of supplying blood to clinicians I feel that a clinical pathologist must reiterate the dangers of blood transfusion, but, having done so, the final decision as to whether to transfuse a patient must lie with the physician or surgeon in charge of the case. Doubtless Mr. Moore had his own good reasons for transfusing blood, and in the unfortunate circumstances of the case I think he is to be congratulated on publishing the facts as another warning of the dangers of blood transfusion.

The case described by Mr. Moore illustrates a rare but alarming complication of incompatible transfusion, of massive blood transfusions, and indeed of certain surgical operations. The existence of this haemorrhagic syndrome must be recognized and appropriate treatment undertaken at an early stage. The case also emphasizes the danger of the clerical or administrative error in blood transfusion work. Most transfusion accidents arise from clerical or administrative errors. It is essential, before any transfusion is given, to read the label on the bottle and to ensure that the identity of the patient about to be transfused agrees with the information given on the matching label on the bottle.

Many surgeons and obstetricians will agree with Admiral Rainsford that moderate blood loss can be treated successfully with plasma or with dextran. More use could be made of these products. In any event, however, the danger to life by withholding blood must be weighed against the risks of transfusion. The final decision as to whether to transfuse must surely rest with the clinician who is accepting full clinical responsibility for the patient.—I am, etc.,

Blood Transfusion Service, West of Scotland Region, Lanarkshire. JOHN WALLACE.

Tuberculous Meningitis after B.C.G.

SIR,—In view of the particular interest aroused by our paper reporting the development of tuberculous meningitis in a baby nine months after B.C.G. (*Journal*, October 25, 1958, p. 1019) we feel that it may be worth while to give a more detailed account of the epidemiology, kindly supplied to us by Dr. W. H. Findlay, area chest physician, Perth.

At Birth (May, 1956).—The child was born on May 13, 1956, and the situation in the family as regards tuberculous infection at this time was as follows. The mother, who was the index case, had had an arrested lesion for some years. Four years previously (August to October, 1952) her sputum was positive for *M. tuberculosis* but has been negative since. From the time of her discharge from hospital (April, 1953) the lesion had remained completely inactive and was considered in a state of complete arrest at the time of the baby's birth (subsequent follow-up confirms this). At the time of writing she has completed a period of over six

years free from infection. The brother (aged 18 years) was known to have a calcified primary complex in the right lung. This had been present and observed at intervals for a period of three years. He had had a routine *x*-ray on March 21, 1956 (i.e., within two months before the baby's birth), which confirmed that the complex had remained healed. (In our original paper it was erroneously stated that he had a lung cavity.) The father was a healthy man who had had one previous "contact" *x*-ray, which was negative. There was no question of his suffering from pulmonary tuberculosis at this time or being a source of infection. The above being all the home contacts, it was considered entirely safe to vaccinate the child at home.

Second Month.—A Mantoux test, 1/1,000 P.P.D., was done on June 26, 1956, with negative result. B.C.G. vaccination (intradermal vaccine) was performed on June 29, and a Mantoux test done on August 22 was positive—induration 9 mm., erythema 12 mm. This result was considered to be in keeping with a normal reaction following B.C.G.

Third to Eighth Months (Inclusive).—The child remained healthy, thriving and increasing in weight normally during this period. The mother had three attendances at the clinic during this period and complete arrest of the lesion was confirmed. The brother had two routine attendances, and it was considered that there was complete arrest of the calcified complex.

Ninth Month (February, 1957).—During this month an independent *x*-ray of the brother, who had reached military age, was arranged by the national service medical board. This raised doubts of active disease adjacent to his old primary infection. He was investigated immediately, and on suspicion of having an active lesion was admitted to hospital on March 23, 1957. Two weeks later *M. tuberculosis* was isolated from sputum culture taken on February 23. The child was probably infected during the weeks around this period. The use of the term "overwhelming infection" may well be justified, as contact was a daily occurrence. During the ninth month the child's father was examined at the clinic following routine mass radiography which had been done in the previous month. A small lesion of "doubtful activity" was noted. Investigation and subsequent follow-up proved this to be inactive, and at the time of writing it has remained unchanged for almost two years. This incident, in our opinion, is of collateral interest only.

Tenth Month (March, 1957).—The child showed signs of failing health during the latter part of this month, and in the following month (April, 1957) she was admitted to hospital suffering from meningitis. Her brother had been previously admitted to chest hospital (tenth month).

Careful scrutiny of these facts brings us to the conclusion that the child most probably contracted infection around the eighth or ninth month of her life, resulting in tuberculous meningitis in the eleventh month.—We are, etc.,

King's Cross Hospital, Dundee.

MARY KERR.
J. M. DUNBAR.

Auto-immune Erythrocyte Sensitization

SIR,—Dr. J. Darnborough, under the heading "A Unique Case of Auto-immune Erythrocyte Sensitization," describes the case of an apparently healthy man who had no significant illness and whose red cells gave a true positive direct antiglobulin test (*Journal*, December 13, p. 1451). Such a finding, although uncommon, is not as rare as Dr. Darnborough's title suggests. Stratton, Stone, and Tovey (1958, unpublished, referred to by Stratton and Renton[1]) have described eight similar cases of positive direct Coombs tests in blood donors. Two of these donors had a previous history of virus pneumonia and one of these has since developed rheumatoid arthritis, but the others were, and have remained, apparently healthy. Indeed, some of them declared that they had never had any illness throughout their lives, and exhaustive tests failed to reveal any abnormalities other than the positive direct Coombs test.

The exact frequency of such cases is unknown, but when they do occur they may give rise to difficulties in blood-grouping procedures. Six of the eight cases were detected, like Dr. Darnborough's case, because of apparent incompatibility by the indirect Coombs technique when cross-matching their blood for transfusion. The remaining two were Rh-negative donors whose blood reacted "positively" when tested against an anti-D serum by the indirect Coombs technique. These samples would have been labelled "D^u-positive" had not a direct Coombs test been carried out, and this latter test is desirable on any sample thought to be D^u-positive.—We are, etc.,

National Blood Transfusion Service, Manchester.

F. STRATTON.

Bristol.

GEOFFREY H. TOVEY.

REFERENCE

[1] Stratton, F., and Renton, P. H., *Practical Blood Grouping*, 1958, p. 74. Oxford.

Foreign Body in the Nose

SIR,—A relative recently told me that she had been advised by her doctor to try and remove a bead from her 3-year-old child's nose with a hairpin. In view of this I suggest a simple and, I think, infallible method of removing a rounded foreign body from the nose of a young child. Toddlers are frequently seen at our Mission hospital in Uganda with groundnuts up their nostrils, and this method, for which I claim no originality, can be carried out by any of our untrained nurses.

Take a Higginson syringe and squirt water up the clear nostril, which will cause the child to cry. Quickly close the nostril by pressure with the finger and the crying of the child will force the water down the other nostril under pressure, pushing the foreign body before it.—I am, etc.,

Church Missionary Society, Ngora, Uganda.

P. B. SPARKE.

Antibiotic Therapy for Bronchitis

SIR,—No one will deny the advantages of any drug that will cut short the duration of illness, but Dr. W. J. Keating seems on insecure ground when he supports antibiotic therapy for bronchitis by reason of the saving of costs of a hospital bed (*Journal*, December 13, p. 1475). Surely "sickness diagnosed as bronchitis" is at the very foundations of family practice and will in most cases be treated at home whatever drugs are used. The argument that prophylactic tetracyclines reduce the cost to the nation of sickness insurance benefit is tempered by the fact that true bronchitis is usually most severe at the extremes of life, and neither the very young nor the elderly draw this monetary benefit.

There are two articles in common domestic use to-day which in the writer's opinion may contribute to respiratory lesions of irritant or infective origin. These are oil convector heaters when used in bedrooms or when faulty, and, secondly, paper handkerchiefs

(" tissues ") drying at the bedside after use. Is there not an opening here for some propaganda to save man-hours, housewives' hours, doctors' visits, and even prescription costs ?—I am, etc.,

Romford, Essex. RICHARD M. S. MATTHEWS.

Proper Use of Words

SIR,—Since the Festive Season was approaching, I carefully included two potential red herrings in my letter (*Journal*, November 29, p. 1359). It is some satisfaction to see both being devoured.

First [*sic*], being aware of Fowler's[1] support of *firstly* I was careful to state that " We might, with De Quincey, detest " it. I gave Osler's brother-Regius as a second authority for doing so. Despite Sir George's opinion to the contrary (*Journal*, December 20, p. 1538), everyone must agree with me that the possibility of detesting exists. Had the detestation been unanimous I should have written " we should " (or would I have written " we would " ?). Fowler splits infinitives unnecessarily (" to wrongly give," p. 570); he sometimes puts a capital letter after a colon (p. 245), sometimes not (p. 305). We might do the same on his authority or we might detest these practices, and everyone must agree with me that those possibilities exist. The function of language is not to convey meaning but to convey the intended meaning correctly.

My second red herring is perhaps a snake in the grass, because I was hopefully aware that someone might misread my last sentence and think that Sir George admires my addresses. Regii, like editors, detest them: my address to the annual meeting of the General Practice Section of the Royal Society of Medicine on " The Physiology of Laughter " remains unpublishable. The difference between " student of Sir George's who admires " and " student of Sir George's, who admires " should leave Dr. W. G. Shakespeare (*Journal*, December 20, p. 1538) in no doubt that I did not accuse Sir George of admiring my addresses. (Fowler recommends " Shakspere.")

Now we can get back to medicine, for which (you probably believe, Sir) medical journals are meant.—I am, etc.,

Oxford. H. M. SINCLAIR.

REFERENCE

[1] Fowler, H. W., *A Dictionary of Modern English Usage*, 1926. Oxford.

POINTS FROM LETTERS

" Flat on Your Back "

Dr. L. D. LORD (Mandeville, Jamaica) writes: I can assure Dr. K. G. Bland (*Journal*, November 15, p. 1229) that his observation of people taking up the prone position when asked to lie on their backs is as valid out here as in Birmingham, and is equally puzzling to everyone here.

Intracranial Haemorrhage and Ketonuria

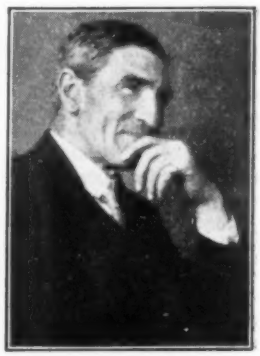
Dr. P. L. DESHMUKH (Poona) writes: Dr. J. MacDonald Holmes in his article on the medical management of subarachnoid haemorrhage (*Journal*, April 5, 1958, p. 788) writes that he has not seen any appreciable degree of ketonuria in the coma of intracranial haemorrhage. My limited experience does not bear this out. I vividly remember about five cases where the practitioner was actually treating the case as one of diabetic coma because there was unconsciousness with gross glycosuria and ketonuria. . . . They were old persons above the age of 60, suffering from cerebral arteriosclerosis or old hemiplegia.

Obituary

H. CRICHTON-MILLER, M.D., F.R.C.P.

Dr. Hugh Crichton-Miller, a noted figure in British psychiatry, and the founder of the Tavistock Clinic, died at Harrow-on-the-Hill on New Year's Day. He was 81 years of age.

Hugh Crichton-Miller was born on February 5, 1877, in Genoa, where his father, the Reverend Donald Miller, D.D., was the Presbyterian chaplain. From Fettes he went to Edinburgh University, where he was president of the Union, obtaining his M.A. in 1898 and his M.B., Ch.B. in 1900. He proceeded to the M.D. in 1902 and in the same year became an M.D. of Pavia University. He took the M.R.C.P. (London) in 1931 and was elected F.R.C.P. in 1939.



After acting as house-physician and house-surgeon in the Edinburgh Royal Infirmary Crichton-Miller took the unusual step of setting up in general practice in two places—San Remo in the winter, and Aviemore, Inverness-shire, in the summer. The number of patients he came across suffering from functional nervous disorders impressed him. Yet no treatment was available for them. In an attempt to provide treatment he gave up general practice and opened Bowden House, Harrow-on-the-Hill, in 1911 as a nursing-home devoted entirely to the treatment of patients with neurosis. Although without formal training, he had an aptitude for this work, and he was familiar with the work of Janet, Freud, Jung, and other Continental workers. Bowden House was unique in this country in those days, and it continues to do its special work. " H. C. M." (as he was known to his friends) maintained an interest in Bowden House till the day of his death.

During the first world war, in the R.A.M.C., Crichton-Miller was officer in charge of functional cases at the 21st General Hospital in Egypt and consulting neurologist, 4th London General Hospital, from 1915 to 1917.

Crichton-Miller was an enthusiast for what he described as " binocular vision "—that is, the need to examine and to treat the physical as well as the psychological aspects of illness. Every patient in Bowden House had a physical examination with biological and pathological tests as well as psychological treatment. Often a patient referred with a label of " Only nerves " was shown to have concurrent organic trouble—a discovery from which H. C. M. derived good-humoured and impish delight.

In 1923 he founded the Tavistock Clinic in London and became its first honorary director, a post he held for many years. At that time the facilities for out-patient treatment in psychotherapy were almost unknown. Undaunted by the difficulties and with the backing of a group of leading physicians in London, Crichton-Miller started the clinic, financing the venture from his own pocket. Bit by bit the medical staff grew and developed, and at the beginning of the second world war the voluntary medical staff and post-graduate students numbered ninety. Crichton-Miller felt almost a missionary zeal to inform, by well-written reports, the doctors who referred cases to the clinic. Sometimes he described his staff as a team of rough riders, but they were in fact carefully selected and did admirable work in the investigation and treatment of patients and in the training

of postgraduate students. Many leading psychiatrists in London to-day took their first steps in psychiatry under the observant eye of H. C. M. in the Tavistock Clinic, which became widely known in this country (and almost better known in the United States). It was the prototype of psychotherapeutic clinics in this and many other countries.

Crichton-Miller was vice-president of the National Association for Mental Health and an active member of its executive committee; a member of the International Committee for Mental Hygiene; a fellow of the British Psychological Society and chairman of the Medical Section; a corresponding member of the Swiss Society of Psychiatrists and a vice-president of the C. G. Jung-Institut, Zurich. As a lecturer he had unusual gifts and was very much in demand at B.M.A. meetings and educational conferences. In 1938 he gave the Charles Hastings Lecture, and a few years before this he had been vice-president of the Section of Neurology and Psychological Medicine at an Annual Meeting of the Association. He was a member of the Psychological Medicine Group Committee for many years.

After the second world war, on the outbreak of which he had been appointed medical officer in charge of the E.M.S. psychiatric hospital at Stanborough, Watford, he was elected president of the Psychiatric Section of the Royal Society of Medicine and also President of the International Society for Psychotherapy.

Crichton-Miller was essentially a pioneer—at times, perhaps, a rather turbulent pioneer. The more conventional psychiatrists of the old school looked with suspicion on his numerous activities, and they were not slow in saying so. They soon discovered that H. C. M. was a great fighter, particularly at meetings of the Psychiatric Section of the Royal Society of Medicine, where he often crossed swords with his critics. In his heyday he was a striking speaker, full of humour—usually well salted—and with a remarkable command of facts, which he produced with relish, often to the discomfiture of his doctrinaire colleagues. A prolific writer, he published a number of books written with the object of presenting "The New Psychology" in non-technical language. In 1912 his book on *Hypnotism and Disease* excited considerable comment. In point of fact it is something of a classic in the vast literature upon hypnotism and contains many original features: he describes, for instance, what was known as "collective hypnotization"—a somewhat daring innovation in those days. Another advance was his use of sedative drugs as an aid to hypnosis and a preparation for suggestion. Thus he anticipated the later technique of narco-analysis. However, he soon abandoned what he regarded as the superficialities of hypnosis in favour of the detailed study and treatment of the sick mind. In 1920 he was editor of the book *Functional Nervous Disease*, which had a considerable vogue. This was followed in 1922 by *The New Psychology and the Teacher* and *The New Psychology and the Parent*. An excellent book in its day appeared in 1930—*Insomnia: An Outline for the General Practitioner*. In 1931 *Marriage, Freedom, and Education* was published, and in 1933 one of his best books appeared, *Psycho-Analysis and its Derivatives*. In addition he wrote a large number of papers in the medical and educational journals.

Dr. Crichton-Miller's wife was the daughter of Sheriff Lorimer, K.C., of Edinburgh. She died in 1954. His youngest son was killed in a bombing mission over Germany. He had five other children. His eldest son Donald (now headmaster of Stowe) gladdened his father's heart by getting his rugger blue at Cambridge and a cap for Scotland. H. C. M., a keen mountaineer, spent many holidays climbing in Skye and in Switzerland.

It is difficult for the present-day psychiatrist to appreciate the importance of Crichton-Miller's early work, coming as it did at a time when mental hospitals had not yet emerged from the era of custodial care. All over the world his former pupils bear witness in their work to his qualities as teacher and friend.—E. A. B.

H. W. writes: When Crichton-Miller was spending his winters on the Italian Riviera and his summers at a Scottish spa he found hypochondriacs at both were only too numerous and therefore set forth to discover fresh ways of treating them. Before 1914 he and Maurice Nicoll had set up in Harley Street as doctors with psychological leanings, much to the fascination of their neighbours, whose noses took an upward slant. He was active at hospitals where "shell-shocked" soldiers were treated during the first world war, and shortly after its conclusion he edited *Functional Nervous Disease*, to which Bernard Hart, W. H. R. Rivers, J. A. Hadfield, and George Riddoch all contributed. At this time he was in much demand at training colleges and universities, giving semi-popular expositions of "The New Psychology," which for him was Jungian in orientation.

Early in the 'twenties he and his supporters leased 51, Tavistock Square, where patients of modest means or wage-earners could be treated by hypnosis, suggestion, persuasion, or such other methods as were then available. Crichton-Miller's drive and that of his henchman of those days, J. R. Rees, gave the Tavistock Clinic the position it gained. It was tolerant towards many different viewpoints, and there was a determination to popularize psychology which thrilled the young and made the cynics scornful. He severed his connexion with it before 1939.

Crichton-Miller combined a Presbyterian rigour with a charm that seems innate in many who have been born and bred north of the Tweed. The charmed followed him; he inspired others to work for the advancement of his "New Psychology" with an ardour that knew no rest but at times generated misunderstanding and spleen. His three books on "The New Psychology" for teacher, parent, and preacher, were much read, as were many other popular articles he wrote. It would be easy to underrate the significance of his work. We are certainly more critical and scientific now. Like other pioneers he had many angular sides; he was not without enemies and detractors; he enthused over endocrines and focal sepsis in ways which one can smile at, but they were part of a defence against the hauteur which some of his enthusiasms aroused. However much one may be sceptical, he contributed a focal point to many who in the inter-war years began to realize and to investigate the connexion between soma and psyche. Psychiatry would have developed differently without him. He had impassioned supporters. The hidden qualities emerged in his last illness, when he who had so often been critical and restless bore the restrictions of a very slowly developing disorder with a tolerance which few who had known him previously would have forecast, and during which his curiosity and alertness of interest seemed little abated.

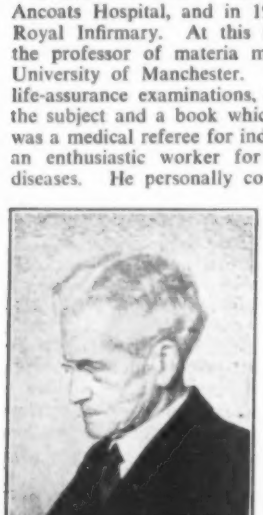
E. M. BROCKBANK, M.B.E., M.D., F.R.C.P.

Dr. E. M. Brockbank, honorary consultant physician to the Manchester Royal Infirmary and historian of Manchester medical institutions, died in a nursing-home on January 2. He was 92 years of age.

Edward Mansfield Brockbank was born in Australia. His family were Quakers, and they came back to England when he was only a child. Educated at Bootham School, York, and at Owens College, Manchester, he graduated M.B., Ch.B. at the Victoria University of Manchester in 1890, proceeding to the M.D., with honourable mention, three years later, and taking the M.R.C.P. in 1894. After a junior resident post at the Manchester Royal Infirmary he worked there as resident medical officer for two years and he was also for a time at Birmingham General Hospital as house-physician. Always a ready writer and interested from an early age in cardiology, he contributed his first article to this *Journal* in 1893 on the subject of "Pulsus Paradoxus in Acute Laryngitis." His book on the diagnosis and treatment of heart diseases ran into six editions, and for many years he was editor of the *Medical Chronicle*, a

journal published in Manchester. He was elected F.R.C.P. in 1907 and appointed M.B.E. in 1920.

Brockbank's first honorary appointment was at the Ancoats Hospital, and in 1905 he joined the staff of the Royal Infirmary. At this time also he was assistant to the professor of materia medica and therapeutics in the University of Manchester. An expert on the conduct of life-assurance examinations, he wrote numerous papers on the subject and a book which was published in 1947. He was a medical referee for industrial diseases, and he became an enthusiastic worker for the prevention of malignant diseases. He personally conducted a successful campaign to prevent mule-spinners' cancer among workers in cotton mills, and he was chairman of the research subcommittee of the joint board of the University of Manchester and the Manchester Cancer Committee. To all other work against cancer in the Manchester area he gave his keen support, being chairman of the local branch of the British Empire Cancer Campaign and a member of the committee of the Christie Cancer Hospital and Holt Radium Institute. His book on mule-spinners' cancer was published in 1941.



A past-president of the Manchester Medical Society and the Manchester Pathological Society, Dr. Brockbank was a tireless worker for the Manchester Medical Library, being its chairman for 45 years. In recent years he had been gathering fresh material about the history of Manchester's medical institutions. A member of the British Medical Association for 65 years, he was secretary of the Section of Medicine at the Annual Meeting held in Manchester in 1902, and president of the Section of the History of Medicine at the Meeting held there in 1929. On that occasion he wrote *The Book of Manchester and Salford*, which was both an entertaining and a learned account of the area which he knew so well.

Of Dr. Brockbank's five children, three were sons and two were daughters. One son, Dr. William Brockbank, is a physician on the staff of the Manchester Royal Infirmary.

We are indebted to Professor J. CRIGHTON BRAMWELL for the following appreciation: It is 46 years ago that I first met Dr. E. M. Brockbank. He was then dean of the "M.R.I.," and his kindly human interest in the welfare and happiness of his students made him admirably fitted for the job. Later, as medical registrar, one of my happiest recollections is the little parties we used to have in his room each morning at 11 o'clock drinking tea and discussing all manner of subjects, ranging from the works of Stephen Leacock to philosophy. I can still see the twinkle in his eye on those occasions, for he had a keen sense of humour. Dining at his house and having lunch with him at the Reform Club were equally enjoyable. He was a very striking and distinguished-looking man, with his slim figure, sharp features, and mass of wavy silvery hair.

After the first world war specialization was not regarded with approval by some senior members of the staff, but Brockbank was not one of those—he was always out to help his junior colleagues. It was he who, in conjunction with A. V. Hill, then our professor of physiology, persuaded the medical board to spend part of its funds on financing a department of electrocardiography, the staff of which consisted of one part-time registrar and one technician-cum-secretary. I well remember at that time receiving, in reply to an application for an extension of leave, a characteristic and cryptic postcard, "E.C.G. O.K. E.M.B." He was delighted when, 25 years later, this became the university department of cardiology.

Brockbank served the medical school well, especially the medical society. For many years he was chairman of the library committee, and when the society was reconstituted he became its first honorary member. Later it must have given him great pleasure when his son, William, was elected president. His book, *The Honorary Medical Staff of the Manchester Infirmary, 1752–1830*, is a valuable record of those early days.

On his 91st birthday he wrote, with his own hand, charming letters of thanks for the good wishes he had received from many of his old students, by all of whom he will be remembered with affection and respect as a true friend and a wise counsellor.

D'ARCY POWER, C.B.E., M.C., M.R.C.S., L.R.C.P.

Air Vice-Marshal D'Arcy Power died at his home at Kingston-upon-Thames on December 26, 1958. He was 69 years of age.

D'Arcy Power was born on June 2, 1889, the elder son of Sir D'Arcy Power, the surgeon and medical historian. After leaving the Merchant Taylors' School he became a medical student at his father's old hospital, St. Bartholomew's. He interrupted his studies to serve with the Montenegrin contingent of the British Red Cross Society during the second Balkan war in 1912–13, being awarded the medal, and then returned to St. Bartholomew's, qualifying M.R.C.S., L.R.C.P. in 1914. On the outbreak of the first world war in that year he was called up as a member of the R.A.M.C. Special Reserve, and served in France and Belgium throughout the war, being awarded the Military Cross in 1916. He transferred to the Medical Branch of the Royal Air Force in 1918, and remained in the Service until 1946, when he retired. He was principal medical officer in the Mediterranean area from 1930 to 1934; in the India and South-East Asia Command from 1942 to 1945; and in Transport Command in 1945. From 1945 to 1949 he was house-governor of the Royal Masonic Hospital, and he was a former chairman of the board of management of the Metropolitan Convalescent Institution, and a former member of the Kingston-upon-Thames borough council. A member of the British Medical Association for 35 years, he was the representative of the Medical Branch of the R.A.F. on the Council of the Association in 1950–1, and at various times had served on a number of committees, including the Armed Forces Committee, of which he was a member from 1947 to 1951. In 1918 he married Miss Cecilia Collins, and had one son and one daughter.

A. R. writes: D'Arcy Power was one of the original officers of the R.A.F. Medical Branch, transferring from the R.A.M.C. when the R.A.F. was formed in April, 1918. His inclinations soon led him towards the administrative side of the Service, which gave scope to his undoubted flair for organization. His most fertile years were almost certainly those just before the second world war and during the early war years, when he was head of M.A.2 in the Air Ministry. At this time the Service was expanding from a few thousand men to a total of about one and a half million men and women. It was largely due to his devoted work during this period that the expansion of hospital facilities proceeded so smoothly and with so little fuss. He left the Air Ministry to become principal medical officer, India and South-East Asia Command, with his headquarters at Delhi. There, even his power of organization and imperturbability were insufficient to offset the peculiar administrative set-up, and he suffered from the constant frustrations and petty annoyances imposed upon him. Many of his colleagues expected—and hoped—that eventually he would become the Director-General of the R.A.F. Medical Services, but, whether it was because of his experiences in India or for some other reason, it was not to be. It was generally believed at the time that he did not wish to be considered for the appointment.

D'Arcy, as he was known to everyone in the Service, was a big, hearty man with a great sense of humour.

During his days at the Air Ministry, when I first came to know him, he had an immense task into which he was putting his whole heart and soul, doing everything in his power to promote the efficiency of his side of the expanding Service. He had nothing of the "passed-to-you" type of administrative medical officer about him, for he never shirked the taking of responsibility. He was always quite ready to discuss the pros and cons of any question, and when he had come to a decision he would defend his position stubbornly, while if convinced by argument that he was wrong he never hesitated to say so. Not the least of his services to the R.A.F. resulted from his close contacts with many of the senior members of the civilian medical profession; it was at a City dinner that he initiated a most fruitful collaboration with a member of the staff of a London teaching hospital. D'Arcy will probably be best remembered for his unfailing cheerfulness and good humour, but behind his joviality was a hard-working and efficient personality whose loyal service during an exceedingly difficult period helped to ensure that the R.A.F. medical service was not found wanting when the days of trial came.

D. McL. writes: Towards the end of the first world war D'Arcy Power was serving with the Royal Flying Corps, and when the Royal Air Force was formed on April 1, 1918, he transferred to the Medical Branch of the R.A.F. Then commenced his long and dedicated service with the R.A.F. He was offered and accepted a permanent commission—one of the "founders" of the Medical Branch. In those early days the new service required officers with outstanding administrative ability. D'Arcy Power fulfilled these requirements to the full, and from 1920 to 1934 he served in administrative posts in Egypt, Iraq, and Malta. 1935 found D'Arcy Power at the Air Ministry as head of the branch responsible for the organization of R.A.F. hospitals, medical attendance services, and rehabilitation units. This period was one of very rapid expansion in the R.A.F., and it was indeed fortunate that an officer of D'Arcy Power's organizational ability was available. The excellent and renowned reputation of the R.A.F. hospital and treatment services during the war is proof of the exceptionally able manner in which he planned and organized the expansion.

In 1940 he was Officer Commanding, Central Medical Establishment, R.A.F., and as such organized the successful "recovery" service for R.A.F. aircrew casualties during and after the Battle of Britain, whereby they received very early specialist treatment, with a consequent saving of many valuable lives. The zeal and efficient manner in which this service was carried out was largely due to the push and energy of D'Arcy Power.

Always unassuming, quiet, and reticent in manner, D'Arcy Power was an excellent administrator, possessed of a lucid brain, with the ability to make up his mind and give rapid decisions. His sense of duty and his energy were remarkable, and infectious to others. He had great personal charm and made friends easily: it was a privilege to be his friend.

SELINA F. FOX, M.B.E., M.D.

Dr. Selina F. Fox, founder of the Bermondsey Medical Mission, died there on December 27, 1958, aged 87.

Selina FitzHerbert Fox was born at Blackheath on April 27, 1871, the daughter of Sir Francis Fox. She was educated at Wimbledon High School and studied medicine at the London School of Medicine for Women and the General Infirmary, Newcastle upon Tyne, graduating M.B., B.S. at Durham University in 1899. She proceeded M.D. in 1903. In 1900 she went out to India for the Zenana Bible and Medical Mission as assistant medical officer at the Lady Kinnaird Memorial Hospital, Lucknow, but her health could not stand up to the climate and she had to return to England. She arrived in Bermondsey in 1901, working at the Church Missionary Society's medical centre. When the work there had to be curtailed Dr. Fox was so concerned with the poverty and need for medical care of the women and children in the area that she founded the Bermondsey Medical Mission in 1904, leasing for the purpose the building in Grange Road that is still part of the Mission Hospital.

The scope of the work at first was mainly that covered by general practice and maternity work, and Dr. Fox and her voluntary helpers became well-known figures in Bermondsey's courts and alleys. As the work grew she saw the need for specialist clinics and later for hospital beds. From this time her aptitude for building and planning, learnt from her famous father, showed itself, and she continued to alter and add to the premises, until the present hospital was opened in 1929 with gynaecological, medical, and surgical beds. These twenty beds were open until after the second world war, when it was thought better to concentrate on the large number of elderly patients in the district who needed hospital care, and the theatre block was consequently adapted to become a ward and bring the total number of beds to thirty. Dr. Fox was appointed M.B.E. in 1938.

When the National Health Service was introduced in 1948, the Mission Hospital was taken over by the Ministry of Health, and, though the Mission's social work and general practice was allowed to continue in the same premises, Dr. Fox, then aged 77, found it very difficult to accept the changing situation, fearing that the change of management would mean an alteration in the religious character of the work. This was understandable, for until this time the work had been mainly planned and developed by her on her own initiative. In later years she became reconciled, realizing that the essential character of the hospital had not changed and that the Mission itself was continuing to grow with the development of its social work for old people and in the opening of residential and convalescent homes.

As a person, Dr. Fox was a typical pioneer woman doctor, indomitable in purpose, full of initiative, perhaps a little isolated from the other social workers in the district, but beloved by her patients, and particularly by those from her early days, and to the end staunch in her witness to the Christian faith.—B. G. M.

LILLIAS B. HARDIE, M.D.

Dr. Lillias B. Hardie, formerly assistant medical officer of health, Kingston-upon-Hull, died on December 11, 1958, during a journey by train from Inverness to London. She was 70 years of age.

Born on August 23, 1888, at Beverley, East Yorkshire, where her father was in medical practice, Lillias Beverley Hardie graduated M.B., Ch.B. at Glasgow University in 1918, and proceeded to the M.D. in 1933.

N. G. writes: Dr. Lillias Hardie's great love for children and her keen interest in their physical, mental, and moral welfare made her choice of a career in the school health service a foregone conclusion. For more than twenty-five years she was an assistant medical officer of health engaged primarily in the school health service of the city of Kingston-upon-Hull, and during the absence on war service of the senior assistant medical officer of health she ably deputized for him during the very difficult and hazardous wartime days and nights in that "north-east coast town." Her professional interests centred mainly on the care and welfare of the handicapped children, and her visits to them in their various reception centres during the war—e.g., to the physically handicapped pupils at Barrow Hall, in Lincolnshire, and to the partially sighted children at Kirk Hammerton, near York—were much appreciated by the children, the parents, and the teachers. Her work for the children in the nursery classes and for the delicate children in residence at the Etton Camp School in the East Riding was of a very high order. When the Hull Training College for Teachers was reopened at very short notice in 1944 with Dr. Helena Todd as principal, Dr. Hardie gave the lectures on health education to the students and continued to take a keen interest in the affairs of the college till ill-health intervened some eighteen months later. Since her

retirement she had been living on Deeside, but had continued to take a lively and personal interest in the educational and medical affairs of Hull. Sincere sympathy is extended to her brother, Mr. David Hardie, consultant ophthalmic surgeon, Bournemouth, and to her sister, Miss Isobel Hardie.

Sir BENNETT HANCE, K.C.M.G., K.C.I.E., O.B.E. M.D., F.R.C.S.Ed.

The obituary of Sir Bennett Hance was printed in the *Journal* of September 20 (p. 745).

Dr. D. C. OZA writes from Morvi, Saurashtra, India: Sir J. B. Hance, when residency surgeon at Rajkot, left with us the happy memories of a delightful personality. I was chief medical officer at Morvi and associated with him many times during his stay at Rajkot, when the whole of Saurashtra was a princely state. We had lively discussions on the medical profession and on what was needed in acute emergencies such as outbreaks of cholera, etc. Sir Bennett had great regard towards the medical profession and acted with us as a medical brother: consequently I was inclined to write these few words, not forgetting him.

Medico-Legal

CONSCIENTIOUS OBJECTION TO TRANSFUSION

[FROM OUR LEGAL CORRESPONDENT]

Last April we printed in this column (p. 838) a note on the prosecution at Nottingham Assizes of a married couple who by reason of their religious scruples as Jehovah's witnesses would not allow their newborn child to be sent to hospital for exchange transfusion, with the result that he died from haemolytic disease of the newborn five days after birth. The judge stopped the case and directed the jury to acquit them of manslaughter when it appeared in evidence that the family doctor had not made it clear to the father that if the child did not go to hospital he would die.

Child Placed in Custody of Children's Society

In similar circumstances in Toronto (*The Times*, December 16, 1958), where a newborn child was in hospital and suffering from haemolytic disease and the parents, who were also Jehovah's witnesses, refused to allow transfusion because of their religious beliefs, action was taken before the provincial juvenile court of Ontario to remove the custody of the child from the parents and to make her a ward of the Children's Aid Society. The matter was dealt with by Judge Lorne Stewart at a special court held in the hospital. Awarding custody to the Society the Judge said that by reason of their refusal to authorize transfusion, even though it was on conscientious religious grounds, the parents were in the legal sense neglecting the child.

A transfusion was given immediately after the court order, the child being already 5 days old. On the following day she was reported to be much better.

If such a situation arose in England it would probably be possible for any interested society or person to take proceedings in the High Court under the Guardianship of Infants Acts and get the matter heard in time by a Chancery Judge, and no doubt equivalent machinery exists in the Scottish Courts. Your legal correspondent knows of no case in which action on these lines has been attempted. A doctor thus faced with the imminent manslaughter of a child by his parents, in addition to communicating with the police as it would be his duty to do, as suggested in our note on the Nottingham case, would be justified in putting the facts before the National Society for the Prevention of Cruelty to Children. After all, the threatened child would be as much his patient as the wrong-headed parents, and infinitely more in need of help. It is to be hoped, however, that the situation will seldom arise.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **December 20** (No. 51) and corresponding week 1957.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	4	1	6	0	1	2	1	3	0	1
Dysentery ..	1,210	92	156	14	8	610	113	163	11	1
Encephalitis, acute	6	0		0		3	1		0	
Enteric fever:										
Typhoid ..	5	1	1	0		2	0	1	0	
Paratyphoid ..	2	0	1 (B)	0		9	0	0	0	
Food-poisoning ..	168	18	21	0		160	19	9	0	
Infective enteritis or diarrhoea under 2 years				16	21				8	29
Measles*	10,113	666	140	40	428	2,435	35	59	43	15
Meningococcal infection	19	1	8	0	1	27	1	8	0	2
Ophthalmia neonatorum	20	3	7	0		22	0	5	0	
Pneumonia† ..	527	32	371	7		699	53	416	3	27
Poliomyelitis, acute:										
Paralytic ..	18	0	1	0	2	33	0	0	2	1
Non-paralytic ..	10	0				18	1			
Puerperal fever§ ..	179	31	23	2	1	166	25	9	1	2
Scarlet fever ..	1,283	85	90	25	32	679	49	81	9	20
Tuberculosis:										
Respiratory ..	479	54	95	17		467	43	94	26	
Non-respiratory	62	8	16	3		42	3	11	2	
Whooping-cough	530	27	50	64	58	451	33	23	1	1

DEATHS	1958					1957				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	No comparable figures available.	0	0	0	0
Dysentery ..	1	0		0			0		0	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0			0	0	0	
Infective enteritis or diarrhoea under 2 years	5	0	1	0	2		0	1	0	0
Influenza	37	3	3	0	1		15	3	0	3
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia ..	778	61	27	26	21		89	38	16	5
Poliomyelitis, acute	4	0		0	0		1		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	112	7	13	3	1		8	11	1	3
Non-respiratory		0	2	0	0		1	0	0	0
Whooping-cough ..	0	0	0	2	0		1	0	0	0
Deaths 0–1 year ..	327	31	32	9	15		25	35	11	10
Deaths (excluding stillbirths) ..	12,440	1033	737	170	199		1176	705	168	187
LIVE BIRTHS ..	13,520	1122	1050	203	306		1155	973	176	316
STILLBIRTHS ..	319	17	23				21	24		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Paratyphoid B at Scarborough

Recently about 30 cases of infection with paratyphoid B, some of them asymptomatic, have been diagnosed at Scarborough, Yorkshire.

Dr. W. G. EVANS (Medical Officer of Health) writes: On December 20, 1958, the pathologist at Scarborough Hospital found a suspicious organism in a stool sent by a general practitioner. The patient was a student nurse at St. Mary's Hospital and was non-resident.

As there had been a number of very mild transient cases of diarrhoea in the female chronic-sick wards in which she worked during the preceding weeks, admissions and discharges in these wards were suspended pending investigation. After confirmation of the diagnosis patients and staff in these wards were swabbed, and 2 nurses and 17 patients were found to be excreting the organisms. All remaining patients and staff in the hospital were then swabbed, and 2 nurses in another female ward and 1 male patient were found to be excreters. The latter had been transferred from an old people's home five days before. All inmates (143) and staff of the home were also swabbed, and 7 symptomless excreters were found. Two days later an inmate whose swab had been negative developed the disease. Since then, 1 more excreter has been found and 1 patient has developed the disease in the second female ward of the hospital.

The hospital and home were originally local-authority hospital and "house" contiguous with one another. They are now run separately except for kitchens and laundry, which serve both. The staff in these departments are not affected. One section of the hospital is occupied by a maternity unit. All staff and patients here are also clear of infection. This unit has continued to function. All other departments of the hospital and home are closed for admissions and discharges.

All outside contacts have so far proved to be negative, but a student nurse at Scarborough Hospital developed the disease on December 27 while on Christmas leave. Her connexion with the outbreak at St. Mary's has not yet been established. All investigations at Scarborough Hospital have so far proved negative. The organism was sent for phage typing and has proved to be an untypable strain. Work on this point is continuing.

The disease in the few frank cases observed has been mild, though the effects in the very old are bound to cause anxiety.

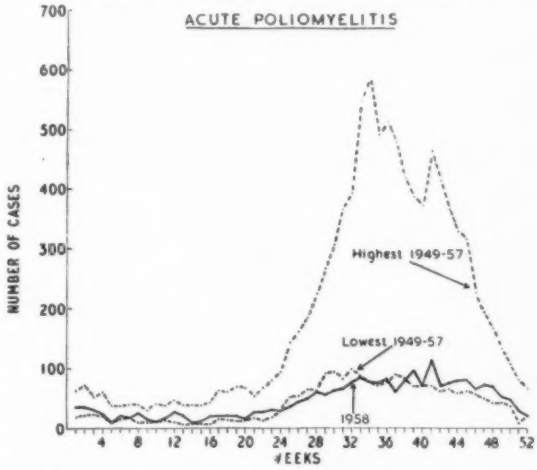
Apart from the initial investigation, the bulk of the bacteriological work has been carried out by the Public Health Laboratory, Hull. Thanks to the co-operation of the consultant in infectious disease in the area, all infectious cases have been removed to infectious disease hospitals. The steps taken to investigate and control the outbreak have all been discussed and agreed by the Control of Infection Committee at Scarborough Hospital. An outbreak of this kind involves a great many individuals and several units of the Health Service. I would like to acknowledge gratefully the excellent co-operation that has been forthcoming from all concerned.

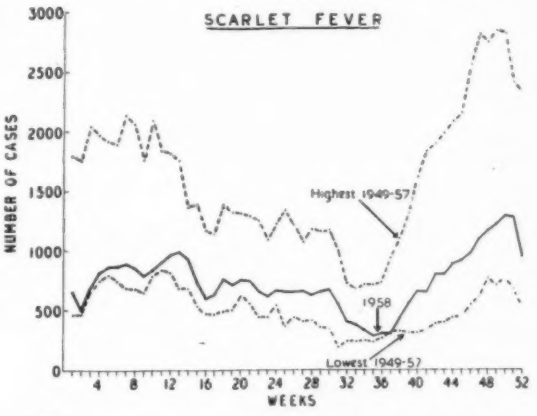
Diphtheria at Wetherby

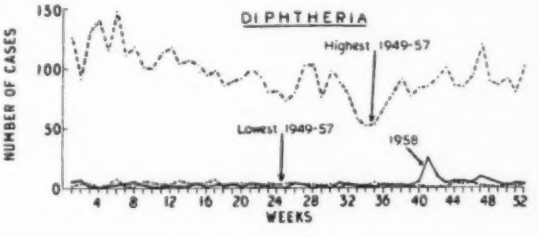
An outbreak of diphtheria comprising 2 clinical cases and 19 carriers has occurred near Wetherby, Yorkshire, at St. John's School for the Deaf. Dr. R. G. SMITHSON, Divisional Medical Officer of Health, reports that on December 5, 1958, laboratory evidence of diphtheria was obtained from a girl aged 12 in the school for the deaf; she had been suffering from a sore throat. The organism was of a virulent mitis strain. Out of the 275 occupants of the school 90 of the nearest contacts were immediately swabbed, and one member of the girl's class was found to be a heavy carrier. The remainder of the school were then swabbed, and 17 more carriers were detected, mainly on the boys' side. Among these carriers was a nun sister-teacher. Immunization injections were given to all concerned, with the exception of 2 who refused. When the school was closed for the Christmas holidays 17 of the children were taken into Seacroft Isolation Hospital. After Christmas, when another swabbing was carried out, the principal of the school and a shoemaker instructor were both found to be carrying the organism. The principal was then admitted to hospital with mild clinical diphtheria. A third swabbing of the school was recently carried out, and the results suggest that the outbreak is coming to an end.

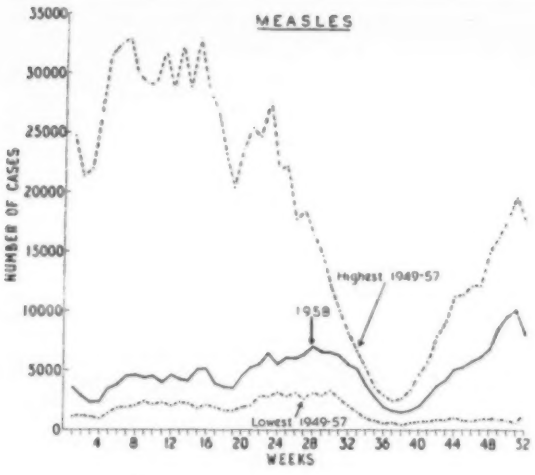
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1949–57 are shown thus ------, the figures for 1958 thus ————. Except for the curves showing notifications in 1958, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Week Ending December 27, 1958

The number of notifications for every infectious disease fell during the week ending December 27 in England and Wales. The largest decreases were 2,102 for measles, from 10,113 to 8,011, 444 for dysentery, from 1,210 to 766, 338 for scarlet fever, from 1,283 to 945, 244 for whooping-cough, from 530 to 286, 118 for acute pneumonia, from 527 to 409, and 72 for food-poisoning, from 168 to 96.

The largest declines in the notifications of measles were 347 in Lancashire, from 1,082 to 735, 233 in Wiltshire, from 483 to 250, 171 in Cheshire, from 534 to 363, 144 in Yorkshire West Riding, from 1,059 to 915, 105 in Glamorganshire, from 157 to 52, 103 in Hampshire, from 220 to 117, and the only exception to the general decline was a rise of 51 in Yorkshire North Riding, from 83 to 134. The largest decrease in the number of notifications of whooping-cough was 27 in Warwickshire, from 41 to 14. The chief fluctuations in the returns for scarlet fever were a rise of 25 in Yorkshire West Riding, from 138 to 163, and falls of 39 in Essex, from 122 to 83, and 29 in London, from 85 to 56. Three cases of diphtheria were notified, being 1 less than in the preceding week.

The notifications of acute poliomyelitis numbered 20, and these were 3 fewer for paralytic and 5 fewer for non-paralytic cases than in the preceding week. The largest returns were 5 in Lancashire and 3 in Yorkshire West Riding.

The chief centres of dysentery were Yorkshire West Riding 129 (Leeds C.B. 45, Earby U.D. 30, Wakefield R.D. 20), Glamorganshire 104 (Cardiff C.B. 63, Rhondda M.B. 32), London 69 (Battersea 13, Islington 11, Deptford 10), Lancashire 63 (Eccles M.B. 17), Hampshire 58 (New Forest R.D. 24, Farnborough U.D. 21), Middlesex 41 (Hendon M.B. 32), Essex 33 (Braintree and Bocking U.D. 11), Surrey 33 (Croydon C.B. 17, Frimley and Camberley U.D. 10), Lincolnshire 29 (Grimsby C.B. 24), Nottinghamshire 25, Staffordshire 23, and Warwickshire 20.

Industrial Accidents and Diseases

The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were reported in November, 1958, was 119, compared with 72 in the previous month and 116 in November, 1957.

The numbers of cases of industrial diseases in the United Kingdom reported during November, 1958, were as follows: Lead poisoning 2, aniline poisoning 1, compressed air illness 1, anthrax 1, epitheliomatous ulceration 15, chrome ulceration 15; total 35. There were no deaths.—*Ministry of Labour Gazette*, December, 1958.

Medical News

Release of Viomycin.—The Ministry of Health and the Department of Health for Scotland announce that viomycin will be available on prescription from February 1.

C.M.O., Ministry of Pensions.—Sir ARTHUR MASSEY, Chief Medical Officer, Ministry of Pensions and National Insurance, is retiring from the public service on March 31. He will be succeeded by Dr. C. G. MAGEE, a Deputy Chief Medical Officer in the Ministry.

Vice-Presidents of Royal Society.—Sir LINDOR BROWN, F.R.S., Jodrell professor of physiology, University College London, and Sir CHARLES DODDS, F.R.S., Courtauld professor of biochemistry, University of London, are among the four vice-presidents of the Royal Society appointed for the period ending November 30, 1959.

Institute of Obstetrics and Gynaecology.—London University announces the appointment of Dr. J. H. M. PINKERTON, senior lecturer at the University College of the West Indies, to the second chair of obstetrics and gynaecology at the Institute, and of Mr. W. G. MACGREGOR, senior lecturer at University College Hospital Medical School (London), to the readership in obstetrics and gynaecology at the Institute.

News of Rheumatism.—The Empire Rheumatism Council proposes to assist general practitioners in keeping abreast of recent advances in this field by sending them quarterly reports. The first of these reports, dated January, 1959, comprises an introductory statement by the president of the council and a signed article on the routine management of rheumatoid arthritis.

Volunteers Still Wanted.—The Common Cold Research Unit at Harvard Hospital, Salisbury, is again appealing for healthy men and women between 18 and 45 as human "guinea-pigs." Comfortable living quarters are provided, and fares to and from Salisbury are paid up to a maximum of £3, as well as 3s. a day pocket money. Full details are obtainable from the medical superintendent of the hospital. So far 5,921 volunteers have visited the Unit, which is run jointly by the Medical Research Council and the Ministry of Health. Summarizing progress in 1958, Dr. C. H. ANDREWES, F.R.S., the Unit's director, said that workers in several countries (U.S.A., Sweden, Denmark, as well as Britain) had cultured a number of viruses from minor infections resembling colds, and, while they had caused some mild symptoms, no evidence had emerged that any of them caused common colds—at best they might account for some more or less "uncommon colds."

Matron of the Middlesex.—Miss MARJORIE J. MARRIOTT, matron of the Middlesex Hospital, was appointed O.B.E. in the New Year Honours. Miss Marriott is also chairman of the Prison Nursing Advisory Board and honorary treasurer of the International Council of Nurses.

Cambridge University.—Dr. B. TOWERS, fellow of Jesus College, has been appointed a university lecturer in anatomy. Dr. J. H. CULLEN has been appointed a senior assistant in research in medical psychology in the department of medicine, and Dr. C. M. CLARKE an assistant in research in medical psychology. The Raymond Horton-Smith prize for 1957–8 was awarded to Dr. R. W. R. RUSSELL.

Birmingham University.—The title of senior clinical tutor has been conferred on Mr. W. B. L. DOWNING, and the title of university clinical lecturer on Mr. H. M. HARRISON (orthopaedic surgery), Dr. B. S. B. WOOD (paediatrics and child health), and Dr. E. H. MUCKLOW (radiology).

Liddle Triennial Prize.—The London Hospital Medical College announces that Dr. D. A. POND, of the department

of psychological medicine, University College Hospital, London, won the 1958 prize for his essay on "The Social and Economic Aspects of Epilepsy." The prize, which is open, is valued at £200. The subject for the 1961 prize is "Mechanisms Involved in Disturbances of Fluid Balance." Further details are obtainable from the dean, The London Hospital Medical College, Turner Street, London, E.1.

Art Prize for Doctor.—The British Art Critics' Prize for 1958 has been awarded to Dr. J. C. SPENCER WELLS. Dr. Wells formerly practised in the Scilly Isles, but at the age of 40 he took up painting. Almost entirely self-taught, he is now regarded as one of the finest of the Cornwall group of artists. He has held one-man shows in London and New York. He is 51.

"Bluebottle."—Surgeon Lieutenant R. R. A. COLES, R.N., has been appointed helmsman of *Bluebottle*, the Dragon belonging to the QUEEN and PRINCE PHILIP.

Professor W. Melville Arnott, professor of medicine at Birmingham University, will be in Northern Nigeria from January 24 to March 6 as a Medical Visitor on behalf of the Colonial Office.

Professor T. P. Kilner, Nuffield professor of plastic surgery at Oxford from 1944 to 1957, has had conferred on him the title of professor emeritus.

Dr. P. J. Kerley, director of the *X*-ray department of the Westminster Hospital, has been elected an honorary fellow of the American College of Radiology.

COMING EVENTS

Goulstonian Lectures.—Dr. W. S. PEART will lecture at the Royal College of Physicians on January 20 and 22 at 5 p.m. His subject will be "Hypertension and the Kidney."

Psycho-analysis and Philosophy.—Professor J. HYPPOLITE, director of the Ecole Normale Supérieure, Paris University, will lecture (in French) at King's College, London, at 5.30 p.m. on March 3 and 4 on "La Psychanalyse et la Philosophie Contemporaine."

"Public Health and the Family Doctor."—Joint conference of College of General Practitioners and Society of Medical Officers of Health, May 23 and 24, at the Wellcome Building, Euston Road, London, N.W.1. Part I, "The New Epidemiology"; Part II, "Family Health"; Part III, "Partners in Social Medicine." Registration (10s.) to the Secretary, Society of Medical Officers of Health, Tavistock House South, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, January 12

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. W. S. C. Copeman: Management of the "Rheumatoid" Patient.

Tuesday, January 13

BELMONT HOSPITAL CLINICAL SOCIETY.—5.30 p.m., debate: Problem of the Psychopath. Speakers, Dr. Maxwell Jones and Dr. Desmond Curran. A discussion will follow.

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—8 p.m., Valedictory Address by Dr. H. E. Haas: Psychotherapy.

KING'S COLLEGE HOSPITAL MEDICAL SCHOOL.—At Medical School Lecture Theatre, 4.30 p.m. 7th Dorothy Platt Memorial Lecture by Mr. Hedley J. B. Atkins: Modern Aspects of the Treatment of Cancer of the Breast.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Watson Smith Lecture by Dr. K. R. Vickers: Place of Dermatology in a General Hospital.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Institute Theatre, 5 p.m., Mr. A. W. Badenoch: Pyelitis of Pregnancy.

UNIVERSITY COLLEGE LONDON.—At Anatomy Theatre, Gower Street, London, W.C., 1.15 p.m., Dr. H. Kalmus: Genetical and Cultural Transmission in Animals and Man.

Wednesday, January 14

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Mr. N. R. Barrett: Foreign Bodies in the Venous System.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. F. R. Kilpatrick: Injuries of the Urinary Tract.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Royal Free Hospital School of Medicine 8 for 8.30 p.m., Dr. Greenwood Wilson: The Doctor and the Royal Commission on the Law Relating to Mental Illness and Mental Deficiency.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. H. A. Sissons: Bone Structure and Bone Disease.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., Watson Prize Lecture by Dr. A. Goldberg: Acute Intermittent Porphyria—A Clinical and Experimental Study.

ROYAL MEDICO-PSYCHOLOGICAL ASSOCIATION: PSYCHOTHERAPY AND SOCIAL PSYCHIATRY SECTION.—At 11, Chandos Street, W., 8 p.m., Dr. Jonathan Gould: Hypnosis and the States of Altered Awareness.

Thursday, January 15

BRITISH INSTITUTE OF RADIOLOGY.—8 p.m., Mr. Rodney Smith: Indications for Cholangiography and Pancreatography; Mr. Eric Samuel: Operative Cholangiography—the Radiological Aspects.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor M. Maizels: The Place of Chemical Pathology in Medicine.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Professor J. S. Mitchell, F.R.S.: The Mechanisms of the Therapeutic Actions of Radiations.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.15 p.m., Dr. L. E. Glynn: Some New Concepts of the Nature of Rheumatism.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—3.45 p.m., Arnott Demonstration by Dr. B. Cohen: Modern Variations of John Hunter's Madder Feeding Experiments.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—7.30 p.m., Dr. P. E. C. Manson-Bahr: East African Kala-azar, with Special Reference to the Pathology, Prophylaxis, and Treatment. A discussion will follow.

ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, 5 p.m., Professor E. Neil: Reflexogenic Areas of the Cardiovascular System.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. Denis Williams: Neurology.

WEST OF ENGLAND CHILD HEALTH GROUP.—At Department of Child Health Lecture Theatre, Children's Hospital, Bristol, 8.30 p.m., Professor A. I. Darling: Preventive Dentistry.

Friday, January 16

FACULTY OF RADIOLOGISTS.—At Royal College of Surgeons of England, 4.30 p.m., Radiodiagnosis Section Meeting. Subject: Clinical Evaluation of Types of Angiocardiographic Apparatus. Speakers, Dr. K. E. Jefferson, Dr. J. N. Pattinson, and Dr. D. McC. Gregg.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. C. Oswald: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., clinical lecture by Mr. G. H. Howells: Orbital Tumours.

LEICESTER CHRISTIAN MEDICAL ASSOCIATION.—At Leicester Royal Infirmary, 8.45 p.m., Round-table Discussion: Criminal Responsibility. Dr. Humphrey Kidd, Mr. Raymond Moore, Reverend Basil Williams, and Dr. C. A. H. Watts (Chairman).

PLYMOUTH MEDICAL SOCIETY.—At Freedom Fields, 8.30 p.m., Sir Cecil Wakeley, Bt.: Some Aspects of Malignant Disease.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. G. H. Wooler: Treatment of Hiatal Hernia with Peptic Oesophagitis. (2) 4 p.m., Dr. A. C. Dornhorst: Pulmonary Physical Signs.

ROYAL MEDICO-CHIRURGICAL SOCIETY OF GLASGOW.—At Royal Faculty of Physicians and Surgeons of Glasgow, 8.30 p.m., Dr. P. Macfarlane and Dr. R. G. Sommerville: Bronchiectasis—a Virus Disease?

Sunday, January 18

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Radiotherapeutic Centre, Addenbrooke's Hospital, symposium, 2 p.m., Dr. J. Wedgwood: Early Diagnosis of Bacterial Endocarditis; 2.45 p.m., Mr. W. S. Foulds: Glaucoma; 3.30 p.m., Mr. R. W. Butler: Osteoarthritis in General Practice; 4.35 p.m., Dr. E. Beresford Davies: Onset of Depression in Middle Age.

APPOINTMENTS

BATTEN, J. C., M.D., M.R.C.P., Part-time Assistant Physician (Consultant), tenable at Brompton Hospital.

MANCHESTER REGIONAL HOSPITAL BOARD.—P. J. L. Sequeira, M.B., B.S., Whole-time Consultant Pathologist, Regional V.D. Serology Department, Withington Hospital; Alan Lorimer, M.B., Ch.B., Whole-time Assistant Pathologist (S.H.M.O.), Salford Royal Hospital; R. W. Starczewski, M.B., Ch.B., Whole-time Assistant Psychiatrist, Prestwich Hospital.

SOUTH-WESTERN REGIONAL HOSPITAL BOARD.—A. J. A. McCormick, M.B., Ch.B., F.R.C.S.Ed., D.O.M.S., Ophthalmologist in Exeter Clinical Area (Torquay)

BIRTHS, MARRIAGES, AND DEATHS

Adams.—On December 21, 1958, at Hayling Island, Hants, Rupert Blake Adams, M.R.C.S., L.R.C.P., of Wimborne, Hayling Island, and M.Y. *Foxglove*, Cannes, France, aged 73.

Astbury.—On December 15, 1958, Thomas Astbury, M.R.C.S., L.R.C.P., of Glamorgan.

Bennett.—On December 27, 1958, at 6, Park Hill Road, Wallington, Surrey, Colin Edward Wilmot Bennett, M.R.C.S., L.R.C.P., late of Forest Hill, London, S.E., aged 91.

Blair.—On December 31, 1958, at Hull, Yorks, Robert Bertram Blair, M.B., F.R.C.S.Ed.

Buchanan.—On December 24, 1958, at The Lodge, South Collingham, Newark, Notts, George Gilbert Buchanan, M.B., Ch.B., D.P.H., aged 59.

Candy.—On January 1, 1959, at Ensom District Hospital, James Robert Candy, M.B., Ch.B., of Tadworth, Surrey.

Lomax.—On December 24, 1958, Arthur Joseph Lomax, M.R.C.S., L.R.C.P., of 1, Ruskin Road, Manchester.

Pinches.—On December 17, 1958, at the Royal Masonic Hospital, London, W., Henry Irving Pinches, M.B., Ch.B., of 4, Collingham Road, London, S.W.

Upward.—On December 29, 1958, at his home, St. Aubins, Sandown, Isle of Wight, Harold Arthur Upward, M.B., B.C., aged 84.

Vosper.—On December 21, 1958, at Stanmore, Middx, Percy Vosper, M.R.C.S., L.R.C.P.

Woolley.—On December 29, 1958, Frederick Henry Woolley, M.R.C.S., L.R.C.P., L.D.S., of Standish House, Stonehouse, Glos, aged 61.

Yuill.—On December 23, 1958, at his home, Mizzen Top, Salterns Way, Parkstone, Dorset, Kenneth Elliott Laird Yuill, M.R.C.S., L.R.C.P., D.T.M.&H.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Oxytocin in Labour

Q.—*(1) Is there any danger to the foetus in the use of oxytocin in the second stage of labour, or for the induction of labour? (2) When oxytocin is given to induce labour, is its use in the second stage contraindicated?*

A.—The only safe method for administering oxytocin before or during labour is by means of a continuous intravenous infusion of a solution not stronger than 5 units per litre of diluent. An initial rate of 16 drops per minute can be gradually increased to a maximum of 40 drops per minute, depending on the reaction of a particular uterus. Any unfavourable response on the part of the uterus or of the foetal heart can be arrested or corrected almost immediately by adjusting the rate of flow; it is this complete control which ensures safety. Provided the supervision is good, an oxytocin "drip" may be given to induce labour or to treat inertia in the first stage of labour. If the uterus remains sluggish it may safely be continued into the second stage of labour, always provided there are no signs of foetal distress. Oxytocin therapy is, however, not usually begun during the second stage of labour. This is not because it is dangerous in itself, but because any delay at that time is usually an indication for forceps delivery. Oxytocin and forceps are not generally alternative lines of treatment; they can, however, be complementary.

When oxytocin has been given for several hours during labour it is a common experience to meet haemorrhage during or after the third stage. Many obstetricians therefore keep the infusion running slowly until the baby is born; they can then immediately open the regulator to impose a strong oxytocic stimulus and ensure that the uterus contracts and retracts during and after delivery of the placenta. For further information on oxytocin infusions reference should be made to a previous question (*Journal*, October 19, 1957, p. 953) and to subsequent correspondence.

Repelling Lice

Q.—*What kind of spray would be effective and unobjectionable in preventing fleas or lice transferring from one person's clothing to another's in a factory where working clothes hang in an open rack in contact?*

A.—It is fairly safe to say that no feasible spray or mist treatment could be relied upon to prevent the movement of parasites from articles of clothing in contact with one another. The impregnations of D.D.T. used to keep our troops from becoming infested in field operations at the end of the second world war were at the rate of 1% on the weight of the garment. Treatments of prisoners of war, refugees, etc., then and subsequently, have used an ounce or two of powder. Both these quantities are very large indeed compared with the amounts likely to settle on garments from an "unobjectionable" mist. Moreover, no insecticide would reach the portions of clothing in actual contact.

A method which deserves consideration is the use of electrically heated vaporizers, which cause continuous, slow evolution of insecticides, either as a vapour (B.H.C.) or as an exceedingly fine aerosol (D.D.T.). To be effective, these vaporizers should operate in a space without too much ventilation. Even an ordinary room may change its air between five and several hundred times a day, so that maximum action is likely with closed windows at night. These vaporizers give off roughly 1 g. insecticide per 24 hours, and for health reasons this should probably be the maximum quantity allowed per 15,000 cu. ft.[1] Although heat vaporizers may be suitable for killing mosquitoes or houseflies in aircraft,[2] it is very doubtful if they would be powerful enough to kill ectoparasites in clothing.

The conclusion seems to be that insecticides do not offer much promise. As an alternative, plywood or plastic barriers could be inserted between clothing racks, or, more simply, the hooks placed further apart. On the whole, it seems unlikely that this could be a serious problem among British workmen. Body lice are now exceedingly rare, except among vagrants, and it appears that fleas are much less common than 20 years ago. Possibly complaints are due to a very small number of chronically infested individuals, and tactful investigations might trace these and make suitable personal treatment possible.

REFERENCES

1 *Soap*, 1952, **28**, No. 8, 149; No. 11, 141.
2 *J. econ. Ent.*, 1953, **46**, 715.

Aetiology of Asthma

Q.—*Is there any evidence to suggest that asthma may be due to a deficiency of available acetylcholinesterase and histaminase?*

A.—The suggestions in the question have been considered for many years, but there is no direct evidence which supports these views. There are many articles on the results of treatment of asthma with histaminase, but the general view is that it is of no value.[1 2] The serum cholinesterase activity in patients ill with asthma, including some during severe attacks, has been found by a number of investigators to be normal,[3] while Michelson and Lowell[4] failed to find any activity characteristic of acetylcholine in the whole blood, plasma, or serum of asthmatic subjects.

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1 Feinberg, S. M., *Allergy in Practice*, 1946, 2nd ed. Year Book Publishing Co., Chicago.
2 Rose, B., *J. Allergy*, 1940, **12**, 441.
3 Vorhaus, L. J., and Kark, R. M., *Amer. J. Med.*, 1953, **14**, 707.
4 Michelson, A. L., and Lowell, F. C., *J. Lab. clin. Med.*, 1956, **47**, 119.

NOTES AND COMMENTS

Sale of Poisons and Dangerous Drugs.—In the article by Professor John Glaister and Dr. Edgar Rentoul entitled "The Control of the Sale of Poisons and Dangerous Drugs" (*Journal*, December 20, p. 1524) reference was made in the penultimate paragraph to the Penicillin Act, 1947, and the Therapeutic Substances (Prevention of Misuse) Act, 1953. It should be noted that these Acts were consolidated in the Therapeutic Substances Act, 1956.

Collected Articles from the "British Medical Journal"

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